Combined kidney-pancreas transplantation

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CASE PRESENTATION

A 42-year-old woman with a history of juvenile-onset diabetes mellitus was referred to University Hospitals of Cleveland for pancreas transplantation. Diabetes was first diagnosed at age 15, and insulin therapy was begun at that time. At the time of her referral, her serum creatinine concentration was 1.4 mg/dl and the creatinine clearance 80 ml/min. Protein excretion was 1.2 g/24 hrs. Diabetic retinopathy, discovered four years earlier, had been treated with laser surgery. A cadaveric pancreatic transplant was performed using pancreaticoduodenocystotomy. The patient’s postoperative course was complicated by a peripancreatic abscess that required surgical drainage on two occasions. The patient was euglycemic and insulin-independent until one month following surgery, when overt hyperglycemia and a relative decrease in urinary amylase excretion prompted a 10-day course of treatment with OKT3 for presumed acute allograft rejection. Her blood sugar level returned to the normal range; five months later, however, a second rejection episode did not respond to treatment with OKT3. The patient’s pancreatic allograft was surgically removed and insulin therapy was renewed.

During the subsequent 18 months, the patient developed peripheral vascular disease requiring a right below-the-knee amputation. During this interval, the patient’s renal function gradually deteriorated, in part because of two episodes of contrast-medium-induced nephropathy following aortography. She developed end-stage renal disease requiring initiation of maintenance hemodialysis.

Two years following the initial pancreatic transplant, the patient received simultaneous kidney and pancreas transplants from one cadaveric donor. Maintenance immunosuppression consisted of cyclosporine, prednisone, and azathioprine. One month following transplantation, the patient was treated with OKT3 for acute renal allograft rejection. Thereafter, she maintained excellent renal allograft function. Glycohemoglobin levels, which had ranged between 8.5% and 9.3% during the six months prior to transplantation, decreased to 4.3% within two months of transplantation. Visual acuity measured within two months after the transplant procedure was 20/300 OD and 20/200 OS.

In the seven years following combined kidney-pancreas transplantation, the patient was readmitted to the hospital on 12 occasions. Three separate hospital admissions were prompted by gross hematuria. Cystoscopic evaluation revealed only acute and chronic inflammation of the bladder mucosa and duodenal cuff. Recurrent hematuria prompted enteric conversion of the pancreatic allograft via a pancreaticojejunostomy approximately six years following transplantation. Two years later, the patient developed gangrene of the left foot, which required a left Syme’s amputation. Five years following kidney-pancreas transplantation, the patient published an autobiography detailing how the transplant had improved her quality of life. At last followup, her serum creatinine concentration was 1.1 mg/dl; glycohemoglobin was 3.8%. Visual acuity was 20/30 OD and 20/25 OS.

DISCUSSION

DR. DONALD E. HRICIK (Professor and Director, Division of Nephrology, Department of Medicine, Case Western Reserve University, Cleveland, Ohio, USA): Transplantation of beta cells, either as part of a vascularized pancreatic allograft or as dispersed islets, remains the only therapy capable of establishing an insulin-independent, euglycemic state in patients with diabetes mellitus. Although vascularized pancreas transplantation has been more successful than islet cell transplantation to date, it requires a major operation. The patient presented here illustrates many of the surgical complications of pancreatic and combined kidney-pancreas transplantation in an individual who also has experienced the major benefits of the operation: insulin independence and an improved quality of life. Despite continued controversy about the benefits and risks of the procedure [1, 2], data from the International Pancreas Transplant Registry indicate that the number of pancreas transplants steadily increased between 1988 and 1996 (Fig. 1). During that time interval, more than two-thirds of the pancreatic transplants were performed as simultaneous kidney-pancreas transplants; the remainder were equally divided between pancreatic transplants performed after prior kidney transplants, and pancreatic transplants performed prior to the development of end-stage renal disease. In this discussion, I will focus on the outcomes, benefits and risks of combined kidney-pancreas transplantation in patients with type-I diabetes mellitus and end-stage renal disease.

Surgical issues

Technical considerations. Since the first pancreas transplant in 1966 [3], considerable debate has focused on how the operation...
should be performed. Currently, the majority of pancreatic transplants in the United States are performed with a simultaneous kidney transplant from the same cadaveric donor using the whole pancreas and a portion of the donor duodenum anastomosed via a pancreaticoduodenocystostomy to achieve exocrine drainage via the bladder [4]. Venous drainage of the pancreas usually is established via the iliac veins into the systemic circulation. As conceived by Nghiem and Corry [5], the main advantage of bladder drainage is that it allows monitoring of the urinary concentration of amylase and other urinary enzymes, and thus permits detection of acute rejection of the pancreas before the development of overt hyperglycemia. Unfortunately, bladder drainage of the exocrine pancreas also produces several urologic and metabolic complications that I will discuss later. Moreover, drainage of pancreatic venous effluent into the systemic venous circulation eliminates the first-pass metabolism of insulin normally delivered to the liver via the portal circulation and produces relative hyperinsulinism. Some centers espouse the use of enteric drainage of the exocrine pancreas and/or venous drainage into the portal circulation [6, 7]. Hughes et al reported improved lipid profiles in pancreatic transplant recipients after portal venous drainage compared to profiles in patients managed with systemic venous drainage [8]. It remains to be determined, however, whether this modification in surgical technique influences the survival of either the allograft or the patient.

Transplantation of a segment of the pancreas (body and tail) continues to be performed at some centers and is the technique employed in rarely performed living-related pancreatic transplants [9]. In segmental pancreatic transplantation, various approaches for handling exocrine pancreatic secretions have included ductocystostomy, ligation of the pancreatic duct, anastomosis to the recipient ureter, or obliteration of the ductal system by injection of synthetic polymers. Among the majority of centers performing transplantation of the whole pancreas via pancreaticoduodenocystostomy, arguments persist about the appropriate size of the duodenal cuff [10] and whether to place the pancreatic allograft in the intra- or extraperitoneal space.

**Complications of bladder drainage.** Complications of pancreatic transplantation related to bladder drainage constitute a major cause of morbidity and occur in more than 40% of kidney-pancreas transplant recipients [11]. Table 1 lists the major metabolic and urologic complications of pancreaticoduodenocystostomy. The most common metabolic complication, metabolic acidosis, occurs in 75% to 100% of bladder-drained patients [7, 12, 13], and results from urinary loss of bicarbonate contained in the exocrine secretions of the pancreatic allograft. Acute and chronic volume depletion and a relatively high incidence of calcium-containing bladder stones undoubtedly are related directly to the loss of sodium and bicarbonate that typically result in a persistently alkaline urine. For unclear reasons, the need for bicarbonate replacement tends to diminish with time after transplantation in most patients.

Wound infections, reported in 26% to 61% of kidney-pancreas graft recipients [12, 14, 15], represent a major cause of postoperative morbidity. The high incidence of wound infection presumably is related to loculated pancreatic surface secretions, but prolonged bladder catheterization, underlying diabetic bladder dysfunction [16], and reflux of urine into the pancreatic allograft all play a role. Wound infection rates appear to be lower when the pancreatic allograft is placed within the peritoneal cavity [9, 15]. Secretion of pancreatic enzymes into the lower urinary tract can cause chemical cystitis or urethritis that sometimes results in severe dysuria or gross hematuria.

These complications occasionally warrant surgical conversion of exocrine pancreatic drainage from the bladder to the intestine via either a jejunostomy or a Roux limb. Stephanian et al reported the need for cystoenteric conversion in 6 of 265 consecutive patients (6%) [17]. The most common indications for conversion were intractable metabolic acidosis and chemical urethritis. Sindhi et al reviewed their experience with enteric conversion for metabolic (65%) or urologic (35%) complications and concluded that the procedure is safe and has little peri-operative risk [18]. Nevertheless, complications of bladder drainage and the occasional need for enteric conversion clearly increase rates of hospital readmission, length of hospital stay, and the cost of kidney-pancreas transplantation when compared with kidney transplantation alone [14].

**Table 1.** Complications of pancreas transplantation using bladder drainage via pancreaticoduodenocystostomy

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<thead>
<tr>
<th>Metabolic</th>
<th>Acidosis (bicarbonate depletion)</th>
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<td>Surgical/urologic</td>
<td>Wound infection</td>
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<td>Urinary tract infection</td>
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<td>Pancreatic fistulae</td>
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<td>Bladder anastomatic leaks</td>
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![Fig. 1. Pancreas transplants performed in the United States between 1988 and 1995 including total number (●), number of combined renal-pancreatic transplants (□), and number of pancreas-only transplants (■).](image-url)
Outcomes

Pancreatic outcomes. The technical success of whole-organ or segmental pancreatic transplantation is limited by early allograft thrombosis, which occurs in 3% to 12% of patients [12, 15, 19]. These early technical failures account, in part, for the observation that one-year pancreatic allograft survival rates are lower than survival rates for the simultaneously transplanted kidney [20] (Fig. 2). Registry data suggest that pancreatic allograft survival in patients undergoing combined kidney-pancreas transplantation is superior to that of patients undergoing pancreas transplantation after kidney transplantation (PAK) or pancreatic transplantation alone (PTA) (Fig. 3). This phenomenon might be explained by a loss of isolated pancreatic allografts resulting from difficulties in diagnosing early pancreatic rejection. It is also possible that the isolated pancreatic allograft is more immunogenic than is a renal or combined renal-pancreatic allograft. It is interesting that HLA matching has improved pancreatic allograft survival after PAK and PTA, but not after combined kidney-pancreas transplantation [21].

Alternatively, a simultaneously transplanted kidney might somehow protect the pancreas from acute allograft rejection. The entrapment hypothesis put forth by Kyriakides et al [22] and Severny et al [23] suggests that immunocompetent cells are diverted to the renal allograft and away from the pancreatic allograft on the basis of higher blood flow rates to the kidney. According to the dilution hypothesis, the presence of two allografts dilutes a fixed number of effector cells generated during acute rejection, thus minimizing rejection of the pancreas after combined kidney-pancreas transplantation [23]. Unfortunately, animal models have not provided consistent data to support either of these hypotheses. In rats, pancreatic allografts are preferentially rejected after kidney-pancreas transplantation [24]. In pigs, a renal allograft appears to protect a simultaneous pancreatic allograft from rejection [25].

In many centers, the most common cause of failure of pancreatic allografting beyond the immediate posttransplant period is death with a functioning graft [26, 27]. Douzdjian and coworkers found that cardiovascular disease was responsible for 60% of deaths in 61 kidney-pancreas recipients [27]. This is all the more remarkable considering that diabetic patients usually are selected for combined kidney-pancreas transplantation based on the absence of pre-existing cardiovascular disease [12]. Future efforts at minimizing cardiovascular disease after transplantation are needed to improve both patient and allograft survival.

Patterns of rejection. Investigators in this field generally acknowledge that pancreatic rejection manifested by overt hyperglycemia is usually far advanced and irreversible. A number of laboratory tests have been used as measures of early pancreatic rejection (Table 2) [28–34]; however, none has been sufficiently sensitive or specific to be a reliable, noninvasive method of diagnosing acute rejection. In patients whose transplant has involved bladder drainage of the exocrine pancreas, a relative decrease in urinary amylase secretion remains the best marker of pancreatic rejection. Benedetti and colleagues studied hypoamylasemia as a predictor of biopsy-proved pancreatic rejection and found its sensitivity to be 100% and specificity to be 30% [28]. Others have argued that the benefit of measuring urinary amylase is limited by large intra- and intersubject variability that might be related to hormonal influences on exocrine pancreatic function [29]. Although pancreatic histopathology is the gold standard for diagnosing rejection, pancreatic biopsies are not widely performed because of the perceived risk of complications such as...
bleeding and allograft pancreatitis. In fact, centers with large experiences (using either cystoscopic or percutaneous pancreatic biopsies) generally report few complications. For example, Klassen et al performed 40 consecutive biopsies in 19 patients and reported only one episode of intrabdominal bleeding and no changes in serum amylase or lipase that might suggest pancreatitis [35].

In recipients of combined kidney-pancreas transplants, acute rejection involving both allografts is readily recognized by an increased serum creatinine concentration, a surrogate marker for otherwise unrecognized pancreatic rejection. Expeditious treatment of such episodes undoubtedly contributes to improved pancreatic survival in recipients of combined transplants, as compared with recipients of isolated pancreatic transplants. However, results from centers using either percutaneous or cystoscopic pancreatic biopsies to diagnose acute pancreatic allograft rejection have clearly shown that pancreatic and renal allograft rejection can occur independently. Klassen et al performed pancreatic biopsies that were clinically indicated based either on a twofold increase in serum amylase or a sustained 50% decrease in urine amylase; acute rejection of the pancreas was found in 27% of the biopsies in the absence of histologic or clinical evidence of renal allograft rejection [35]. The same group recently reported a relatively high incidence of late pancreatic rejection episodes (defined as occurring more than one year post transplant), especially in patients receiving low doses of immunosuppressants [36]. Other centers performing serial “protocol” biopsies have reported as much as an 18% incidence of occult acute rejection of the pancreas [37, 38]. Although short-term pancreatic allograft survival is inferior to the survival of simultaneously transplanted renal allografts, recent data from single centers suggest that pancreatic allograft half-life exceeds that of the renal allografts (Fig. 4) [39, 40]. These observations suggest that, in contrast to renal allografts, pancreatic allografts are relatively resistant to chronic rejection. Patients who have returned to chronic dialysis as a consequence of chronic renal allograft rejection but who have retained functioning pancreatic allografts are not uncommon. Management of immunosuppression represents a unique challenge in such patients because of the concomitant effects of uremia on the immune system.

Renal outcomes. Although a simultaneous kidney transplant might protect the pancreas from acute rejection, most [14, 15, 41–43] but not all [44] investigators agree that acute renal allograft rejection rates are higher after combined kidney-pancreas transplantation than in diabetic or nondiabetic control groups who receive kidney transplants alone. The notion that transplanted pancreatic tissue increases the immunogenicity of a simultaneous renal allograft is supported by observations from Carroll et al, who reported a 100% rate of renal rejection in 9 patients who received combined kidney and islet cell transplants [45]. Animal models have not been helpful in explaining this phenomenon. For example, renal allograft rejection rates in pigs are no different after kidney-pancreas transplantation than after kidney transplantation alone [25].

Some centers have reported lower rates of renal allograft [46, 47] or patient [48, 49] survival after combined kidney-pancreas transplantation. However, registry data indicate that short-term renal allograft survival in combined kidney-pancreas transplant recipients is either comparable [50] or superior [51] to that in diabetics receiving a kidney alone (Fig. 5). Thus, somewhat surprisingly, higher rates of acute renal rejection after kidney-pancreas transplantation do not seem to affect at least short-term renal survival rates.

Studies of renal function, as measured by serum creatinine concentrations or other estimates of glomerular filtration rate, generally have indicated no differences between diabetic patients receiving a combined renal-pancreatic transplant or a kidney alone [52–55]. However, these studies have been limited by inclusion of either small numbers of patients or selected patients followed for relatively short periods. Few studies to date have

![Fig. 4. Patient (■), pancreatic allograft (●), and renal allograft (*) half-lives as determined by linear regression. (Reprinted with permission from Ref. 40.)](image)

![Fig. 5. Renal allograft survival in patients who received cadaveric kidneys between 1987 and 1993 in the U.S. Kidney-pancreas recipients (■); kidney-alone recipients with end-stage renal disease secondary to glomerulonephritis (○); kidney-alone recipients with end-stage renal disease secondary to diabetes mellitus (△). (Adapted with permission from Ref. 20.)](image)
employed reliable estimates of glomerular filtration rate to compare renal function in diabetic recipients of kidney or kidney-pancreas allografts. El-Gebely and colleagues, using the clearance of 99mtechnetium to estimate glomerular filtration rate, concluded that renal function was comparable in diabetic recipients of a kidney or a kidney and pancreas [55]. However, follow-up was limited to two years following transplantation. More important, patients in each group were selected on the basis of equivalent number and severity of acute rejection episodes. These selection criteria neutralize the importance of acute rejection on long-term renal function.

Considering the many known or suspected factors influencing long-term kidney survival in renal allograft recipients, the fact that renal function in kidney and pancreas recipients is comparable to that in recipients of only a kidney is probably fortuitous. Compared to diabetics receiving kidneys alone, recipients of both organs tend to have fewer HLA matches and more HLA mismatches with their donors [43, 56], probably because HLA matching is given less priority in allocating the combination of organs. Because of higher rates of rejection, kidney-pancreas recipients often receive higher doses of nephrotoxic immunosuppressants such as cyclosporine [55, 56]. On the other hand, delayed graft function is much less common in kidney-pancreas recipients [43, 56], probably because of shorter cold ischemia times. Thus, the potential deleterious effects of poorer HLA matching and higher rates of acute renal rejection on long-term renal function appear to be balanced by very low rates of delayed graft function and the presumed benefits of euglycemia in preventing recurrent diabetic nephropathy.

Effects on glucose homeostasis

Glycemic control. The importance of glycemic control in slowing the progression of nephropathy and other long-term complications of diabetes mellitus has been validated by the Diabetes Control and Complications Trial [57]. After technically successful pancreatic transplantation, patients with type-I diabetes mellitus achieve a return to normal or near-normal fasting plasma glucose levels, glucose tolerance tests, and levels of glycosylated hemoglobin [58–62]. These patients thus become insulin independent for indefinite periods. The range of blood sugar concentrations observed during 24-hour metabolic profiling in pancreas or kidney-pancreas recipients exceeds that of normal individuals, but peak levels tend to decrease significantly over time [61], as do glycosylated hemoglobin levels (Fig. 6) [62]. Long-term followup studies indicate that insulin independence can be sustained for at least 5 years such that 60% to 92% of kidney-pancreas recipients exhibit glycosylated hemoglobin levels within the normal range 5 years after pancreatic transplantation [60, 61]. Moreover, reversible pancreatic rejection episodes do not adversely affect long-term glycemic control [62].

The euglycemia achieved after kidney-pancreas transplantation reflects a complex interplay among several factors, including the functioning mass of beta cells, hyperinsulinemia (particularly in patients with systemic venous drainage of the pancreas), the diabetogenic effects of immunosuppressive drugs, alterations in counterregulatory hormones, the effect of denervation of the allograft, and the prevailing level of renal allograft function. Corticosteroids [63], cyclosporine [64], and tacrolimus [65] each adversely affects glucose tolerance. Indeed, insulin resistance induced by these drugs occasionally negates the benefit of functioning beta cells and results in type-II diabetes mellitus [66]. The gradual improvement in glycemic control observed more than one year after transplantation [61, 62] probably reflects a reduction in the dosage of these immunosuppressants over time.

Hyperinsulinemia. In kidney-pancreas recipients with systemic venous drainage of the pancreatic allograft, the insulin response to a glucose challenge is two to four times greater than that observed in nondiabetic subjects [67]. Although hyperinsulinemia probably results from decreased hepatic clearance of insulin (because of systemic venous drainage), the rise in insulin levels also might reflect drug-induced insulin resistance or reduced insulin clearance in patients with impaired renal allograft function. In addition, denervation of the pancreatic allograft can lead to incomplete suppression of insulin secretion in response to elevated circulating insulin levels [68].

Despite circumstantial evidence to the contrary in animals [69] and in patients with type-II diabetes mellitus [70], no evidence has proved that hyperinsulinemia contributes to cardiovascular morbidity after kidney-pancreas transplantation. A cause-and-effect relationship is possible, however. Portal venous drainage might alleviate hyperinsulinemia, but the procedure can be technically difficult, and its routine use in kidney-pancreas transplantation might increase surgical morbidity. Furthermore, in a dog model, portal venous drainage did not entirely eliminate hyperinsulinemia [71]. The benefits and risks of portal pancreatic venous drainage clearly warrant further study.

Counterregulatory mechanisms. Conventional treatment of diabetes mellitus with exogenous insulin frequently is complicated by hypoglycemia, which accounts for as many as 4% of deaths in patients with insulin-dependent diabetes mellitus [72, 73]. Moreover, intensive treatment regimens increase the frequency of severe hypoglycemic episodes two- to fourfold compared to conventional therapy [72]. Patients with type-I diabetes mellitus commonly have deranged counterregulatory responses to hypoglycemia, including defective glucagon and epinephrine responses, that can increase the intensity and risk of hypoglycemic episodes [74, 75]. An important feature of counterregulation is the reversal of insulin-induced suppression of hepatic glucose production. When insulin is infused into healthy subjects, it rapidly suppresses hepatic glucose production, thereby reducing the
plasma glucose level [76]. However, mobilization of hepatic glycogen and de-novo synthesis of glucose usually prompt a rapid rebound in hepatic glucose production. The latter response is impaired in diabetics and can be explained by derangements in the secretion of glucagon and epinephrine [77].

Metabolic studies have produced conflicting data regarding the integrity of counterregulatory mechanisms after kidney-pancreas transplantation. Diem et al demonstrated significant improvement, but not normalization, of glucose recovery following insulin-induced hypoglycemia in pancreas transplant recipients when compared to diabetic nonrecipients and normal controls [78]. Improvement was largely related to a marked increase in basal and stimulated glucagon levels, an increase that could be related to systemic venous drainage of the pancreas and elimination of first-pass hepatic metabolism of glucagon. On the other hand, Battezzati et al demonstrated prolonged suppression of hepatic glucose production and a blunted glucagon response to insulin-induced hypoglycemia in kidney-pancreas recipients, which was comparable to that observed in a uremic diabetic control group [79]. The clinical implications of these observations remain unclear.

We have observed frank hypoglycemia in occasional kidney-pancreas recipients, most commonly among those in whom steroid therapy has been withdrawn (unpublished observations). In these cases, hypoglycemia rarely has been associated with severe symptoms and generally is self-limited; this finding suggests that counterregulation is sufficient to prevent severe manifestations of hypoglycemia.

Effects on diabetic complications

In the absence of a randomized controlled trial comparing kidney-pancreas transplantation to kidney transplantation alone or to dialetic therapy, demonstrating the efficacy of pancreatic transplantation in the prevention or resolution of secondary diabetic complications has proved difficult. The popular decision to perform combined kidney-pancreas transplants in patients with advanced nephropathy (often coexistent with other secondary complications) ironically might account for difficulties in demonstrating a benefit of pancreatic transplantation. Conversely, few transplant centers have been willing to expose diabetic patients to the risks of life-long immunosuppression for a pancreas transplant in the absence of the need for a concomitant kidney transplant. The influence of pancreatic transplantation on the complications of diabetes mellitus needs much further investigation.

Diabetic nephropathy. Histologic signs of diabetic nephropathy can be seen in normal kidneys transplanted into diabetic patients as early as two years after transplantation [80]. Bilous and coworkers, who performed renal allograft biopsies on patients who received a pancreatic transplant after prior renal transplantation, reported that the mesangial expansion and increased mesangial volume seen in diabetic patients after renal transplantation alone was prevented [81]. Similarly, Wilczek et al have shown that a pancreatic allograft prevents the development of recurrent diabetic nephropathy in a simultaneously transplanted kidney [82]. Although these studies suggest that a well-functioning pancreatic transplant can prevent recurrent diabetic nephropathy in a transplanted kidney, we have little evidence that euglycemia achieved after pancreatic transplantation can reverse established lesions of diabetic nephropathy in native kidneys. Fioretto et al found that, in nonuremic patients with insulin-dependent diabetes mellitus, mesangial expansion progressed after pancreatic transplantation and was no different than that observed in persistently hyperglycemic control patients who did not undergo transplantation [83]. Pancreatic transplantation in nonuremic patients also requires exposure to nephrotoxic immunosuppressants, such as cyclosporine or tacrolimus, which can accelerate progression of the underlying diabetic nephropathy.

Retinopathy. Ramsay et al compared the eyes of 22 pancreas recipients followed for more than one year after transplantation with the eyes of 16 patients with failed pancreatic transplants [84]. No significant differences appeared in the groups after 24 months; a trend toward improvement after 36 months was not statistically significant. Although this important study suggested that pancreatic transplantation neither reverses nor prevents the progression of diabetic neophopathy, it is clear that longer followup in a larger cohort of patients is required to verify or refute that conclusion.

Neuropathy. Kennedy et al measured nerve conduction, evoked potentials, and Valsalva ratios in 61 patients before and after pancreatic transplantation and compared these parameters in nonuremic diabetics who were awaiting or who had failed a pancreatic transplant. These authors reported statistically significant improvements in the patients with successful pancreatic transplants [85]. Hathaway and colleagues have suggested that pancreatic transplantation improves autonomic neuropathy, as evidenced by improvements in Valsalva ratios [86] and in gastric emptying [87].

Accelerated vascular disease. Whether a pancreatic transplant can prevent the progression of arterial occlusive disease remains to be determined. However, recent studies have documented improvement in diabetic microangiopathy after pancreatic transplantation. Abendroth et al reported a significant increase in transcutaneous oxygen tension in kidney-pancreas recipients when compared to that in diabetic patients receiving a kidney transplant alone [88]. Cheung and colleagues demonstrated increases in capillary size and density following successful pancreatic transplantation [89]. Difficulties in demonstrating a benefit of pancreatic transplantation in retarding the progression of microvascular or macrovascular complications of diabetes mellitus likely are related to persistent elevations of advanced glycation end products despite “correction” of diabetes and renal failure after kidney-pancreas transplantation [90]. Our group has tracked the tissue and plasma concentrations of the pentose-derived glycation end product pentosidine after kidney or kidney-pancreas transplantation in patients with diabetes mellitus. Pentosidine levels are elevated in diabetic patients with normal renal function and in diabetic as well as nondiabetic patients with end-stage renal disease [91, 92]. The combination of diabetes mellitus and renal failure raises the pentosidine content of plasma and tissue to a level higher than that observed in either condition alone [91].

It is not clear whether pentosidine accumulates during renal failure because of its underexcretion or overproduction. Nevertheless, the patient with diabetes mellitus can develop an overwhelming burden of advanced glycation end products after kidney failure ensues. We have shown that both renal and kidney-pancreas transplantation are accompanied by a dramatic, but incomplete, reduction of plasma pentosidine concentrations within three months [93]. By contrast, levels in skin collagen are unchanged or increased as long as 80 months after transplantation (Fig. 7) [94]. Thus formation of advanced glycation end products...
can continue despite otherwise successful kidney or kidney-pancreas transplantation. We and others have shown that plasma levels of advanced glycation end products correlate inversely with glomerular filtration rate [94, 95]. Impaired renal allograft function thus theoretically can negate the benefit of functioning beta cells after kidney-pancreas transplantation.

Quality of life. Patients with successful pancreas transplants usually report an improvement in quality of life [96–98]. Gross and Zehrer polled 65 patients with functioning pancreatic allografts and compared responses with those from 66 patients whose grafts had failed. A higher percentage of patients with functioning allografts reported greater overall satisfaction with life (68% versus 48%; \( P < 0.01 \)), a sense of better health since transplantation (89% versus 25%; \( P < 0.001 \)), and the renewed ability to care for themselves and perform their routine daily activities (78% versus 56%; \( P < 0.001 \)) [97]. In our experience, almost 90% of kidney-pancreas recipients have been able to return to work or school [12].

In summary, pancreatic transplantation is being performed with increasing frequency worldwide. In theory, the benefits of euglycemia achieved after a technically successful pancreas transplantation would be best appreciated if the procedure were performed in patients without renal impairment; however, combined kidney-pancreas transplantation is performed much more commonly in patients with end-stage diabetic nephropathy because physicians are reluctant to use potent immunosuppressive drugs in diabetic patients before they need a concomitant renal transplant. Kidney-pancreas transplantation is clearly associated with rates of surgical morbidity that exceed those observed after kidney transplantation alone. Proven benefits of kidney-pancreas transplantation include insulin independence and an improved quality of life. Because kidney-pancreas transplantation usually is reserved for patients with advanced secondary complications of diabetes, it has been more difficult to prove that this operation arrests long-term diabetic complications. The future of pancreatic beta-cell transplantation resides in its application to diabetic patients before they develop secondary complications. This goal likely will require the development of safe immunosuppressant agents that do not promote glucose intolerance or other risk factors for cardiovascular disease, now the leading cause of death and graft loss after kidney-pancreas transplantation.

QUESTIONS AND ANSWERS

DR. JOHN T. HARRINGTON (Dean, Tufts University School of Medicine, Boston, Massachusetts): Don, it’s great to have you back here. Thanks for a superb review. Let me begin by asking about the current status of islet cell transplantation.

DR. HRICIK: Several factors continue to limit the success of islet cell transplantation. Dispersed islet cells are far more immunogenic than islet cells transplanted as part of a vascularized allograft. In addition, a critical number of islets are required to assure independence from insulin. It has proved to be difficult in practice to obtain this number from single donors. Currently, the use of multiple human donors to harvest islets would limit the supply of whole organs. Xenotransplantation of islets is a logical alternative that has not yet been perfected. Hyperglycemia per se is toxic to the islet cells. Even if an adequate number of islets are transplanted, persistent hyperglycemia can lead to a vicious cycle in which the available islets fail as a result of “metabolic exhaustion.” Despite these limitations, several centers remain interested in islet cell transplantation, and a small but increasing number of patients have maintained long-term insulin independence after islet cell transplantation using currently available technology and immunosuppressive drugs. Most transplant physicians and surgeons would readily welcome successful islet cell transplantation as an alternative to whole-organ transplantation.

DR. NICOLAOS E. MADIAS (Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts): I have two questions. First, you mentioned that several studies have shown improved quality of life in recipients of combined kidney-pancreas transplants. Indeed, it must be a remarkable change to develop independence from insulin for people who for most of their lives had been dependent on the daily insulin injection. On the other hand, you mentioned that there has been significant morbidity in these patients with combined organ transplantation. Has there been any rigorous analysis of mortality and morbidity in comparable patients who received either a kidney or kidney-pancreas transplant?

DR. HRICIK: To the best of my knowledge, a randomized trial has never been performed to allow such rigorous comparisons. Thus, most studies comparing outcomes of kidney and kidney-pancreas transplant recipients are biased by the tendency to select healthier diabetic patients for the combined procedure. Most centers, including our own, exclude patients from kidney-pancreas transplantation if they are over the age of 50 or if they have significant cardiovascular disease.

DR. MADIAS: My second question relates to the so-called protective effect of the kidney on pancreas rejection. Are there any animal studies or studies of human pancreatic biopsies that have examined the expression of immunomodulating molecules in pancreatic tissue in the settings of pancreas alone versus pancreas-kidney transplant? Also, could you comment more on the discrepancy in acute allograft rejection between animal and human kidney-pancreas transplantation?

DR. HRICIK: It is possible that humans differ from animals in terms of the differential expression of major histocompatibility
 antibodies and other immunomodulating molecules after a kidney-pancreas transplant, but I am not aware of studies investigating this possibility. The discrepant rates of acute allograft rejection noted in human versus animal studies could reflect the bias of physicians to more aggressively diagnose and treat acute rejection in kidney-pancreas transplant recipients. On the other hand, it is hard to ignore the fact that virtually all centers have found higher rates of acute rejection in these patients.

DR. ANDREW J. KING (Division of Nephrology, New England Medical Center): In my limited experience with patients who have had a pancreas transplant, it can be difficult to maintain their plasma bicarbonate in a reasonable range. Could you give us some insight into your approach to this problem? The chronic acidosis these patients suffer might contribute to malnutrition by altering muscle metabolism, as well as lead to metabolic bone disease. Have you encountered these chronic complications in your long-term pancreas recipients?

DR. HRICIK: The metabolic acidosis sustained in patients who are recipients of bladder-drained pancreatic allografts can be profound and difficult to treat. Studying the impact of the acidosis on bones in these patients is quite difficult because of the compounding effects of underlying renal osteodystrophy and of immunosuppressive therapy. Moreover, in our experience, pancreatic bicarbonate wasting appears to subside with time in the majority of patients, suggesting that the exocrine function of the pancreatic allograft somehow involves even when the organ’s endocrine function remains intact.

DR. KING: My second question relates to the strategies for immunosuppression in pancreas transplantation. In view of the high rates of rejection reported in these patients, has immunosuppression been modified for pancreas or kidney-pancreas recipients?

DR. HRICIK: In most transplant centers, kidney-pancreas recipients are treated more aggressively than are kidney-alone recipients. For example, we continue to use polyclonal antibodies for induction therapy in all kidney-pancreas recipients but now avoid antibody induction in kidney transplant recipients who exhibit good immediate renal allograft function. Some centers have reported excellent results and lower acute rejection rates in kidney-pancreas transplantation using tacrolimus as a substitute for cyclosporine [99]. Interestingly, overt hyperglycemia has not been a problem in this early experience despite the well-known diabetogenic effects of tacrolimus.

DR. RONALD D. PERRONE (Division of Nephrology, New England Medical Center): Could you comment in more detail about the reversibility of diabetic complications? Is there a threshold at which one might assume that the complications are irreversible? Has enough experience accumulated that allows us to make any judgments about that?

DR. HRICIK: It could be argued that pancreas transplantation should be performed long before the development of diabetic complications. However, few transplant physicians are willing to subject diabetic patients to the side effects of immunosuppression unless it is deemed necessary for a concomitant kidney transplant. In the absence of adequate data to determine whether diabetic complications can be reversed by pancreas transplantation, I think it would be premature to establish arbitrary clinical thresholds beyond which the procedure would be avoided.

DR. AJAY SINGH (Division of Nephrology, New England Medical Center): You indicated that the kidney and pancreas are not equally vulnerable to acute rejection. Is the same true for chronic rejection?

DR. HRICIK: Our experience differs from that of Walker et al [36], who recently described their experience with late pancreatic allograft rejection episodes (occurring more than 12 months after transplantation). In our experience, late loss of a pancreatic allograft is rare, occurring in less than 3% of patients. It is now recognized that immunologic as well as nonimmunologic factors contribute to chronic allograft dysfunction. The observation that chronic renal rejection can occur in the absence of chronic pancreas rejection in a patient who has received both allografts from the same donor tends to suggest that nonimmunologic factors are more important than immunologic factors in the clinical expression of chronic renal allograft rejection.

DR. HARRINGTON: I assume that the gross histologic findings of acute rejection of the pancreas and the kidney are similar. Are there any differences in the kinds of cells that might preferentially attack the pancreas or kidney, or are they the same?

DR. HRICIK: The sequential histopathologic changes of acute rejection in the pancreas have been best studied in animal models [100]. To my knowledge, cellular subtypes are no different than those observed in renal allograft rejection.

DR. ANDREW S. LEVEY (Division of Nephrology, New England Medical Center): Thank you for summarizing the data, limitations, and interpretation of these uncontrolled studies. Would you agree with the conclusion that combined kidney-pancreas transplantation is an expensive and morbid procedure that appears to affect primarily the quality of life? Our current practice selects people who may derive the least benefit from persistent euglycemia. If we expanded the recipient pool to include all type-I diabetics with renal failure, and even all type-I diabetics with renal disease, we would surely face a shortage of pancreases. Is this approach going to remain a niche therapy applicable to only the few people who receive combined kidney-pancreas transplants? Or are we perfecting surgical and immunosuppressive techniques so we can eventually apply them to the larger population of type-I diabetics?

DR. HRICIK: Improvements in surgical techniques or immunosuppressive therapy will have little impact on the shortage of cadaver donors. This shortage remains the most important reason why kidney-pancreas transplantation can be offered to only a limited number of patients with diabetes. If safer immunosuppressive drugs were available, pancreas transplantation might be offered to patients earlier in the course of their disease, but this would only magnify the donor shortage by increasing the pool of candidates.

DR. MADIAS: It is somewhat surprising that renal function in kidney-pancreas transplant recipients is not different than that in control groups despite a high incidence of acute rejection. Have long-term followup studies been performed to verify that this is the case beyond two post-transplant years?

DR. HRICIK: We have recently compared long-term renal function, estimated by the slopes of iCr versus time, in kidney and kidney-pancreas transplant recipients followed for as long as 5 years [101]. A statistically insignificant trend toward more rapid deterioration of renal function in the kidney-pancreas group suggested that the negative effects of acute rejection outweigh the benefits of the concomitant pancreas transplant over long periods. In this analysis, early acute rejection episodes, defined as occurring within the first 3 months after transplantation, had little
impact on long-term renal function compared to later rejection episodes.

Dr. Mark E. Williams (Director of Dialysis, Beth Israel-Deaconess Medical Center West, Joslin Diabetes Center, Boston): I have two questions. First, let me move from abstract philosophy to pragmatic philosophy. For more and more patients with renal failure, living donors are the solution to prolonged waiting for cadaver organs. How do you counsel diabetics with renal failure who have available living kidney donors with regard to pancreas transplantation?

Dr. Hricik: I strongly advise them to consider a living-donor kidney transplant as the first option for at least three reasons. First, the long-term success of kidney transplantation is clearly superior after living-donor transplantation. Second, with currently available immunosuppression, more centers are willing to offer a pancreas-alone transplant from a cadaver donor following a live-donor kidney transplant. Finally, our experience tracking AGE levels after transplantation suggests that the reduced burden of AGEs after kidney-pancreas transplantation derives predominantly from normalizing glomerular filtration rate.

Dr. Williams: I think it’s important that you highlight the ongoing problem of cardiovascular disease in these recipients. Our own data suggest that peripheral vascular disease leading to amputation, which your patient experienced, is accelerated. Have you evaluated specific risk factors? Hyperlipidemia would be one aggravated by both the drugs and hyperinsulinemia. What is your specific clinical approach in these patients? Specifically, how attentive are you to the pretransplant evaluation of peripheral vascular disease, and how do you monitor patients post transplantation?

Dr. Hricik: All our patients are evaluated noninvasively with Doppler scanning of the iliac vessels to determine their suitability for the required vascular anastomosis. Although some centers have reported improvement in microangiopathy after pancreas transplantation [88, 89], I am unaware of studies that have compared macrovascular complications in kidney versus kidney-pancreas recipients.

Dr. Madias: Is recurrent autoimmune diabetes an issue for the patient with a grafted pancreas, or is the immunosuppressive regimen fully protective?

Dr. Hricik: The immune autoreactivity against beta cells in patients with type-1 diabetes is life-long. Unless immunosuppression is employed, the disease will recur in a pancreatic allograft [102]. However, it is generally believed that the level of immunosuppression required to prevent allograft rejection far exceeds that required to prevent recurrence, so this is not a practical issue.

Dr. Madias: You mentioned an increasing tendency of surgeons to perform enteric drainage of the pancreas. Has the issue of surgical technique, that is, bladder versus enteric drainage, been examined prospectively regarding patient and graft survival?

Dr. Hricik: There has never been a randomized trial, but the International Pancreas Transplant Registry recently reported data covering a 2-year span from 1994 to 1996 [103]. During that time, the rate at which enteric drainage has been performed has increased from 2% to 27%. However, there were no statistically significant differences in graft or patient survival.

Dr. Madias: I found the data on pentosidine very interesting. Could you address the discrepancy between your data and those of Dr. Vlassara’s group showing rapid normalization of serum AGE levels after kidney transplantation?

Dr. Hricik: The discrepant results might be related to differences in the assays employed to measure AGEs. The antibodies used in the ELISA that Vlassara and her colleagues have employed recognize AGEs bound to peptides of various sizes. Small peptides with molecular weights of 1000 kD to 3000 kD are normally filtered by the kidney, can be retained in patients with renal failure, and return to normal when renal failure is corrected after transplantation. Pentosidine is a small molecule that modifies proteins of all sizes. It is measured chemically (by HPLC) after complete hydrolysis of peptides and proteins. Although plasma pentosidine levels closely correlate with estimates of glomerular filtration rate, it seems intuitively unlikely that the decrease in plasma levels after renal transplantation could result from the sudden filtration of macromolecules. It is more likely that the correlation between AGE levels and renal function reflects overproduction of these compounds in renal failure and not underexcretion.

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REFERENCES


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