THE END OF DIABETES AND KIDNEY FAILURE: PANCREAS AND KIDNEY TRANSPLANTATION

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This is to acknowledge that Dr. Miguel Vazquez has not disclosed any financial interests or other relationships with commercial concerns related directly to this program. Dr. Vazquez will be discussing off-label uses in his presentation.

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KIDNEY FAILURE AND DIABETES

The prevalence of kidney disease continues to increase in the population, and recent reports estimate that there are 20 million individuals with chronic kidney disease in the United States.[1] Patients with chronic kidney disease are not only at risk for progression to kidney failure but also have a much higher risk for premature death than the general population.

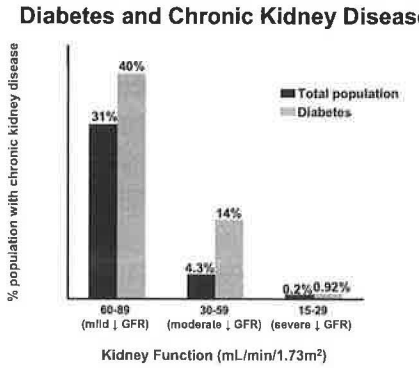


Figure 1

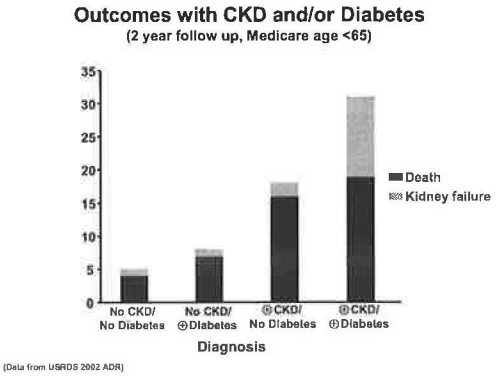


Figure 2

The prevalence of diabetes is also increasing, and it is estimated that 18 million Americans have diabetes.[2] There is a faster growth of chronic kidney disease prevalence among diabetics compared to non-diabetics.[1,3,4] (Figures 1 and 2) As a consequence, the incidence of kidney failure from diabetes continues to increase. For the year 2001, close to one-half of all patients initiating therapy with dialysis for kidney transplantation had diabetes as a primary cause of kidney failure.[1] (Figure 3)

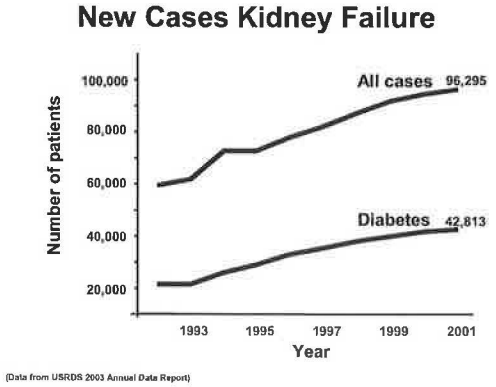


Figure 3

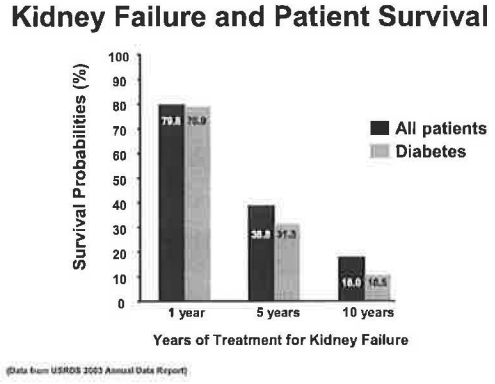


Figure 4

Diabetic patients with kidney failure experience high morbidity and mortality. Coronary artery disease, cardiomyopathy, peripheral vascular disease, retinopathy, neuropathy, autonomic dysfunction, myopathy, depression, and other complications associated with diabetes persist and/or progress during treatment for kidney failure.[5,6] Diabetic patients with kidney failure have higher mortality rates from cardiovascular disease and infections.[1,5,6] (Figure 4) Diabetic patients on dialysis are more likely to discontinue dialytic therapy compared to non-diabetic patients.[5,6]

TRANSPLANTATION OPTIONS FOR THE DIABETIC PATIENT

Dialysis or kidney transplantation prolong life in patients with kidney failure. Most diabetic patients with kidney failure in the US are treated with dialysis.[1] Kidney transplantation, however, offers higher survival rates, better rehabilitation, and improvements in quality of life compared to dialysis.[1,5,7,8]

Diabetic patients also have the option of pancreas transplantation to achieve normoglycemia and independence from insulin.[9,10] The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive therapy with insulin delays the onset and slows the progression of diabetic nephropathy, retinopathy, and neuropathy in patients with type 1 diabetes.[11] The beneficial effects of intensive therapy of diabetes with insulin occur in association with near-normoglycemia.[11,12] The objectives of pancreas transplantation are to achieve normoglycemia and insulin independence, improve quality of life, and ameliorate secondary complications of diabetes.[9,10]

Transplantation of pancreatic beta cells as part of a vascularized allograft or as dispersed islets are currently the only two therapies that can reliably achieve normoglycemia by reestablishing endogenous insulin secretion responsive to normal feedback regulation.[10,13-15] Vascularized pancreas transplantation is an accepted therapy for diabetic patients who require renal replacement therapy.[10,16] Pancreatic islet cell transplantation holds great promise in the treatment of diabetic patients, but is still considered an experimental procedure.[10,15]

Transplantation for Patients with Diabetes

1. **Kidney Transplant Alone (KTA)**
   (a) Living Donor Kidney (LDK)
   (b) Deceased Donor Kidney (DDK)
2. **Simultaneous Pancreas Kidney (SPK)**
3. **Pancreas After Kidney (PAK)**
4. **Pancreas Transplant Alone (PTA)**
5. **Islet Transplant (IT)**

Table 1

Diabetic patients can undergo different transplantation procedures. (Table 1) *Kidney transplantation alone (KTA)* can be performed from a living donor *(living donor kidney transplantation – LDK)* or from a deceased donor *(deceased donor kidney transplantation – DDK)*.

In *simultaneous pancreas and kidney transplantation (SPK)*, the pancreas transplant is performed at the same time as the kidney transplant in diabetic patients with kidney failure. Only one surgical procedure is required, and immunosuppression is used to prevent both pancreas and kidney allograft rejection.[9,17,18] Most simultaneous pancreas kidney transplantations are performed using organs from deceased donors. SPK transplants using a kidney from a living donor and a pancreas from a deceased donor in the same surgical procedure offer the potential advantage of shorter waiting times, lower rates of delayed function of the kidney allograft, and expansion of the pool of available organs.[19] SPK transplantation from a single living donor using one kidney and a segment of the pancreas from the same living donor is another option.[9,20] Potential advantages include better matching, lower risks of rejection, and elimination of waiting time. The main disadvantage is the risk of hemipancreatectomy for the donor and risk of future development of diabetes in the donor. This procedure is uncommon.

Pancreas after kidney transplantation (PAK) is performed in diabetic patients who have previously undergone kidney transplantation.[9,21,22] The main advantage of PAK transplantation is the ability to use a kidney from a living donor with its associated excellent short- and long-term graft survival (in those patients with a potential living donor for a kidney available) followed by

a pancreas transplant from a deceased donor.[22] The main disadvantage is that it involves a second surgical procedure. In addition, the recipient is exposed to antigens from two different donors.

Pancreas transplantation alone (PTA) is solitary transplantation of the pancreas and is used mainly in individuals who have not suffered from extensive and organ damage from diabetes and can potentially benefit from the prevention of future diabetic complications.[9,17,23] The main concerns for this group of patients relate to the risk of surgery and post-transplantation immunosuppression. PTA is considered for patients who have frequent and severe metabolic complications, incapacitating clinical and emotional problems with exogenous insulin therapy, and consistent failure of insulin-based therapy to prevent acute complications.[10]

The field of beta-cell replacement with *islet transplantation (IT)* has advanced tremendously in recent years.[15,24] At the present time, islet transplantation is still considered an experimental procedure.[10] Some excellent reviews have been recently dedicated to this topic.[15,25]

Reports from the Organ Procurement and Transplantation Network/Scientific Registry of Transplant Recipients (OPTN/SRTR) and the International Pancreas Transplant Registry (IPTR) show that the number of diabetic patients receiving transplants has progressively increased in the last decade.[26,27] (Figure 5) Most of the increase in the number of kidney transplants alone (KTA) has been from the large increase in the number of transplants from living donors. The total number of pancreas transplant procedures has increased, although the total number of SPK transplants has declined slightly, while the number of solitary pancreas transplants has continued to grow.

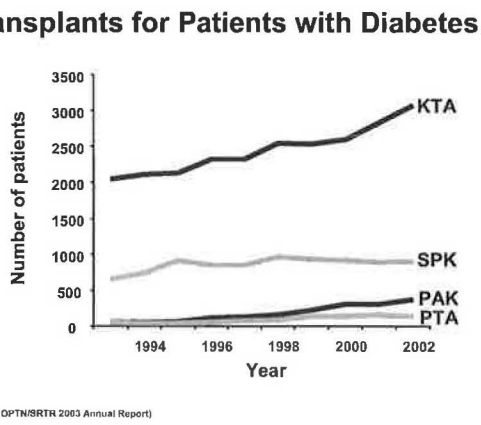


Figure 5

The Transplantation Procedure

The first successful KTA transplant was performed in 1954.[28] It was almost two decades before the benefits of kidney transplantation for diabetic patients were recognized by the transplantation community.[29] Kidney transplantation is now accepted as the preferred renal replacement therapy for type 1 and type 2 diabetics who are able to undergo surgery and take immunosuppressive medications.[16,30]

In most recipients of a KTA, the allograft is placed in the right (or left) iliac fosa of the recipient in an extraperitoneal location.[31,32] In special circumstances, intra-abdominal location of the allograft is necessary. The donor renal artery is anastomosed to the right external iliac artery or hypogastric artery of the recipient. Venous drainage of the allograft is usually via the external iliac vein of the recipient. Urinary drainage is via anastomosis of the donor ureter into the recipient bladder. In special cases, the donor ureter may drain via a ureterostomy into a mobilized native ureter of the recipient.

The first pancreas transplant was performed in the University of Minnesota in 1966.[33] Progress was initially slow due to low rates of patient and graft survival. Advances in immunosuppression, surgical techniques, and medical management of transplant recipients have made possible the enormous progress in pancreas transplantation in the last three decades.[9,34,35]

Several excellent reviews describe the technical aspects of pancreas transplantation.[34-36] The pancreas allograft with a small portion of duodenum from the donor is usually placed intraperitoneally in the right iliac fosa. In combined pancreas-kidney transplantation, the kidney is usually placed intra-peritoneally in the contralateral iliac fosa.

The arterial anatomy is reconstructed, performing a Y graft using the donor iliac arteries in which the donor hypogastric artery is anastomosed to the splenic artery and the donor external iliac artery is anastomosed to the superior messenteric artery.[36] The final arterial anastomosis is performed with the donor Y graft end-to-side to the recipient's right external iliac artery or common iliac artery.

Venous drainage is usually from the portal vein of the pancreatic allograft end-to-side to the external iliac vein of the recipient.[36] This systemic venous drainage of the pancreas is associated with hyperinsulinemia, as insulin bypasses degradation by the liver.[34]

There are several options for drainage of the exocrine pancreas. In the early days of pancreas transplantation, duct occlusion, free intraperitoneal drainage, and enteric drainage of the exocrine pancreas were accompanied by multiple complications.[37,38] Enteric drainage modalities were associated with high rates of anastomotic leaks, abscess formation, and sepsis.[38]

The introduction of bladder drainage (BD) of the exocrine pancreas was a major step in the progress of pancreas transplantation in the 1980s.[39] In bladder drainage, the donor pancreas with a segment of donor duodenum containing the exit of the pancreatic duct is anastomosed side-to-side to the bladder of the recipient (pancreaticoduodenocystostomy). Anastomotic leaks commonly associated with rejection of the donor duodenum are less frequent in the setting of bladder drainage of the pancreas. Another advantage of bladder drainage of the pancreas is that monitoring of urinary amylase can help detect pancreas graft rejection.[38,40] Bladder drainage of the pancreas is, however, associated with significant morbidity. Medical complications related to the urinary loss of sodium and bicarbonate contained in pancreatic secretions include volume depletion and non-anion gap metabolic acidosis.[41,42]

Urologic complications from BD of the pancreas occur from prolonged exposure to pancreatic enzymes and persistently alkaline urine and include urinary tract infections, hematuria, duodenitis, bladder stones, cystitis, urethritis, reflux pancreatitis, and urine leaks.[13,43-45] Chronic complications of bladder drainage lead to conversion from bladder drainage to enteric drainage in close to 12% of patients by two years after pancreas transplantation.[26]

Enteric drainage (ED) of the pancreas avoids the metabolic and urologic complications of bladder drainage. Two important advances have made the widespread change to enteric drainage possible. First, advances in immunosuppression have led to reductions in the rates of acute rejection of the pancreas.[13] Second, the use of pancreatic allograft biopsies makes it possible to reliably diagnose rejection even when urinary amylase cannot be monitored in the setting of enteric drainage of the pancreas.[40,46-48]

In enteric drainage, the pancreas allograft with a segment of donor duodenum is anastomosed side-to-side to the recipient's small bowel (usually jejunum).[22,36] In some cases, the donor duodenum is anastomosed distally end-to-end to a diverting Roux-en-Y limb of recipient jejunum.[42,49] In portal venous and enteric drainage (PE), the portal vein of the pancreas graft is anastomosed end-to-side to a major tributary of the superior mesenteric vein of the recipient.[42,49] Patients with portal enteric venous drainage do not have the levels of hyperinsulinemia seen in patients with systemic venous drainage.[41]

Although uncommon until the mid 1990s, enteric drainage is now the most common method for drainage of the exocrine pancreas.[26] Portal enteric venous drainage is used in >20% of cases

with enteric drainage. Short-term results of pancreatic transplantation using bladder drainage, enteric drainage, and portal enteric venous drainage of the pancreas are similar.[26,50,51].

Allograft Outcomes

Kidney transplant allograft outcomes are excellent. One year kidney graft survival rates for diabetic patients are close to 90% for DDK recipients and close to 95% for LDK recipients.[27] (Figure 6) For SPK recipients, the kidney allograft one year graft survival rates also exceed 90%.[27]

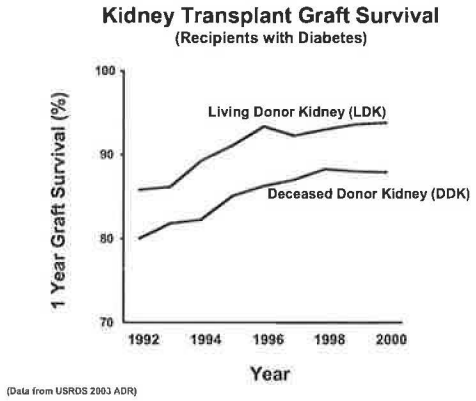


Figure 6

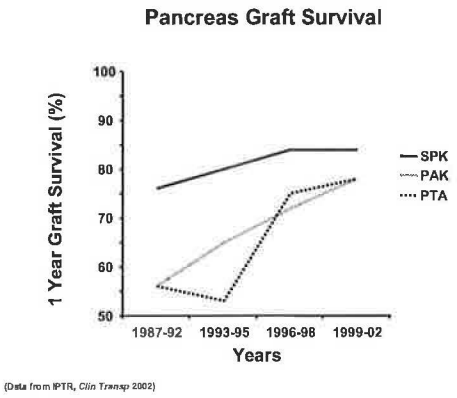


Figure 7

Pancreas allograft outcomes have also progressively improved for all categories (SPK, PAK, PTA) in the last decade. Currently, the one year pancreas graft survival rates are as high as 85% for many patients.[26] (Figure 7) SPK transplant recipients have the best pancreas graft survival rates.

The majority of pancreas transplant recipients have type 1 diabetes, but the proportion of primary pancreas graft recipients reported to have type 2 diabetes was 6% for the year 2000-2001.[26] Pancreas graft survival rates appear to be the same for recipients with type 1 or type 2 diabetes.[26,52]

Pancreas Graft Loss
1. Death with a functioning graft
2. Technical failure
3. Immunological loss
4. New onset type 2 diabetes

Table 2

Pancreas Graft Loss

Pancreas graft failure can occur because of patient's death with a functioning transplant, technical/surgical complications, immunological reasons (rejection or recurrence of autoimmune diabetes), or development of type 2 diabetes. (Table 2)

Death with a functioning graft

Patient survival at one year after surgery now exceeds 94% for recipients of pancreas transplants.[26,27] Nevertheless, death with a functioning graft is still one of the most important causes of pancreas graft loss, especially after the early period. Cardiac-cerebral-vascular disease is the most common cause of death at all times after pancreas transplantation.[26] Infection is the second most common cause of death, with a relatively higher proportion of deaths from infection occurring early after transplantation.

The most important factors predicting higher mortality after pancreas transplantation are older recipient age (older than 45 years), duration of diabetes greater than 25 years, longer time on dialysis waiting for a transplant, and failure of the kidney or pancreatic allografts.[18,53]

Technical failures/surgical complications

Technical failure rates have decreased significantly in recent years but are still the most important cause of pancreatic graft losses, with rates of 8% in the current era.[26] The most common reasons for technical failures are graft thrombosis, infection, pancreatitis, anastomotic leaks, and bleeding. The incidence of these complications was highest in the past for pancreas transplants with enteric drainage, but with improvements in donor/recipient selection, immunosuppression regimens, and surgical techniques, all surgical complications associated with transplantation are becoming less frequent.[54] Factors which have been associated with increased risk of technical failures include donor age above 45, donor death from cardiovascular causes, increased pancreas preservation time, and increased recipient body mass index.[26] Donor obesity also increases the risk for surgical complications.[55,56]

Immunological graft losses

Rejection

Acute rejection is a serious complication of pancreas transplantation, and, in earlier reports, acute rejection was the most important cause of graft loss, both short- and long-term.[38] The incidence of acute rejection has progressively decreased with the introduction of newer immunosuppressive strategies. Administration of induction therapy and the use of mycophenolate mofetil, tacrolimus, sirolimus, changes in steroid regimens, and administration of donor bone marrow, among others, have been effective in reducing the rates of acute rejection and improving graft survival.[57-63] The percentage of technically successful pancreas lost to acute rejection (censored for death with graft function) is as low as 2% for recipients of SPK, 5% for recipients of PAK, and 7% for recipients of PTA.[26]

The lower rate of immunological graft losses due to acute rejection for recipients of SPK illustrates the importance of early recognition of acute rejection in the improvement in graft survival for pancreas transplant recipients. Acute rejection usually involves both the kidney and the pancreatic allografts. Increases in serum creatinine can be the first sign of rejection affecting both organs.[14,64]

Monitoring of urinary amylase is useful in the diagnosis of rejection in pancreas recipients with bladder drainage.[40] Early diagnosis of rejection in all pancreas recipients, and especially recipients of PAK or PTA, is facilitated by the use of pancreatic allograft biopsies.[46-48,65,66] Multiple other methods to diagnose pancreatic rejection have been proposed, including monitoring of serum amylase and lipase, insulin release after intravenous glucose/glucagon, and MRI imaging, but they lack optimal sensitivity and specificity.[14] Hyperglycemia is usually a late event in pancreas rejection, as the exocrine pancreas and acinar cells are the initial targets in pancreas rejection.[67,68]

As long-term pancreas graft survival rates have improved, chronic rejection has become the second most important cause of graft loss in some centers.[69] The most

significant risk factors for chronic rejection include prior episodes of acute rejection, solitary pancreas transplantation, CMV infection, re-transplantation, and one or two antigen mismatches at the B loci.[69]

Recurrence of autoimmune diabetes

Type 1 diabetes is an autoimmune disorder in which the beta cells that produce insulin are selectively destroyed.[70] Type 1 diabetes has recurred in the setting of pancreas transplants between identical twins when no immunosuppression was used.[34,71] Although uncommon, recurrent autoimmune diabetes has also been reported in recipients of pancreas transplants from deceased donors.[72,73] In one report, gradual deterioration in beta cell function with a progressive decrease in C-peptide concentration correlated with the appearance of markers of humoral autoimmunity (antibodies against islet cells and glutamic acid decarboxylase).[72] At the same time, there was histologic evidence of insulitis with selective destruction of beta cells and preservation of alpha and delta cells.

A recent study examined antibody reactivity (by measuring antibodies against glutamic acid decarboxylase and protein tyrosine phosphatase IA-2A) in recipients of pancreas allografts.[74] In a small proportion of patients, there was stimulation of islet antibody reactivity, which was almost invariably followed by a progressive decline in beta cell function and need for resumption of insulin therapy. The pattern of islet antibody reactivity was characteristic of that found in preclinical type 1 diabetes and suggested a role of recurrent autoimmunity in the failure of the pancreas allograft.

Development of type 2 diabetes

New onset type 2 diabetes can be the cause of hyperglycemia after pancreas transplantation.[75] Recipients of SPK transplants have reduced insulin secretory capacity and evidence of insulin resistance.[76] Glucose homeostasis is obtained with increased proinsulin secretion and increased insulin secretion rates.[77] Hyperinsulinemia is common in pancreas transplant recipients. Possible contributing factors to hyperinsulinemia include peripheral insulin secretion without first-pass hepatic insulin extraction, drug-induced peripheral resistance to insulin, denervation of the pancreas allograft, and decreased renal clearance of insulin in some patients.[13,77]

In addition to contributing to peripheral insulin resistance, high doses of immunosuppressive drugs such as cyclosporine, tacrolimus and steroids can be associated with structural damage to beta cells.[78] Recognition of type 2 diabetes after pancreas transplantation is particularly important, as cell damage and hyperglycemia may be reversible (at least in the early stages).

Metabolic Control

A functioning pancreas transplant results in independence from insulin.[10] Fasting plasma glucose levels, hemoglobin A1c (HbA1c) levels, and oral glucose tolerance tests normalize in most patients and have been shown to remain normal or near normal for long periods of time after pancreas transplantation.[79-81] (Table 3) Hyperinsulinemia is present in pancreas transplant

Pancreas Transplantation and Metabolic Control

Time after transplant (n=96)	Pre-transplant	1 year	5 years
FPG (mg/dL)	--	85	88
HbAIC (%)	9.0	5.3	5.2
Acute glucagon response to arginine (pg/mL)	116	292	281

(Data from Robertson et al., *J Investig Med* 44:549, 1996)

Table 3

recipients (especially with systemic venous drainage of the pancreas). C-peptide levels are similar to normal controls.[79]

Type 2 diabetic patients who undergo SPK transplantation may show impaired insulin secretion and worsening insulin resistance initially after transplantation with subsequent improvements.[82]

Hypoglycemia may occur after pancreas transplantation, but it is usually of limited clinical impact.[83,84] Glucose counterregulation is abnormal in patients with long-standing diabetes. Pancreas transplantation restores hypoglycemia-induced glucagon secretion and hepatic glucose production.[85] Epinephrine responses and symptom recognition to hypoglycemia also improve after pancreas transplantation.[86]

Pancreas transplantation improves lipid profiles with higher HDL-cholesterol and significantly lower triglycerides and cholesterol/HDL-cholesterol levels noted early after transplantation.[87] Nevertheless, elevated insulin levels, lipoprotein lipase, and cholesteryl ester are present in these patients.[88]

BENEFITS OF PANCREAS AND KIDNEY TRANSPLANTATION

Patient Survival

Multiple reports have shown that patients with diabetes and kidney failure who undergo kidney transplantation have higher survival rates compared to the survival rates seen for diabetic patients on dialysis.[1,27,89] The one year graft survival rate for diabetic patients undergoing kidney and/or pancreas transplantation exceeds 94% compared to less than 80% for diabetic patients treated with dialysis. Nevertheless, most studies comparing the survival of patients treated for kidney failure with dialysis or kidney transplantation have been limited by a selection bias, as younger and healthier patients usually undergo transplantation while the older and sicker patients remain on dialysis.[5]

Using data from the United States Renal Data System (USRDS) and the Transplant Scientific Registry of the United Network for Organ Sharing (UNOS), Wolfe and colleagues compared the mortality rates of recipients of a first kidney transplant from a deceased donor with that of patients on dialysis on the waiting list for kidney transplantation.[7] This approach reduces the selection bias of comparisons between transplant recipients and dialysis patients who may not be healthy enough to undergo transplantation. As expected, the patients eligible for transplantation were healthier and had a 49% lower mortality than those who were not on the waiting list for transplantation. Patients undergoing kidney transplantation had a higher mortality rate early after transplantation (related to surgery and high intensity immunosuppression). (Table 4) By 18 months after transplantation, however, recipients of a kidney transplant had a mortality risk estimated to be 68% lower than that for patients on the waiting list. The projected increase in life span conferred by transplantation was ten years. Diabetic patients had a 73% reduction in their mortality risk by 18 months after kidney transplantation compared to those diabetic patients remaining on dialysis on the waiting list. The projected increase in life span for all diabetic

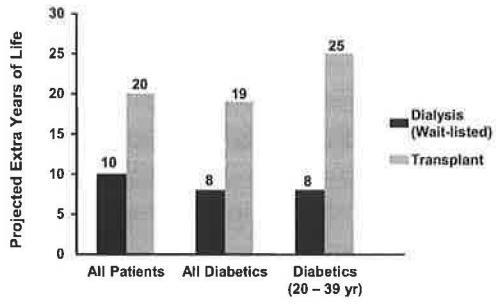
Relative Risk of Death After Kidney Transplantation
(Reference: Wait-Listed Patients)

Time After Transplant	0 – 30 Days	>365 Days (Cumulative)
All Patients		
US	2.43	0.32
Canada	2.91	0.25
All Diabetics		
US	1.94	0.27
Canada	1.87	0.38
Diabetics 20-39 yr		0.18

(Data from Wolfe et al., *NEJM* 314:1725, 1999 and Rabat et al., *JASN* 11:917, 2000)

Table 4

Projected Years of Life
Dialysis vs. Transplantation



(Data from Wolfe et al., *NEJM* 341:1725, 1999)

Figure 8

patients was 11 years, and the projected increasing life span for young diabetics (20-39 years of age) was 17 years. (Figure 8) A similar report from Canada also confirmed a long-term survival benefit for kidney transplantation compared with remaining on the waiting list on dialysis, with a 75% reduction in the relative risk of death by one year after transplantation.[90] Patients with diabetes had a 62% lower mortality risk with a kidney transplant as compared to remaining on dialysis on the waiting list. (Table 4)

Although in the absence of a randomized trial it is difficult to establish causation between kidney transplantation and superior survival for diabetic patients with kidney failure, it is unlikely that such a study will ever be conducted.[8] The observations of the great benefit of transplantation upon survival for diabetic patients with kidney failure makes transplantation the preferred renal replacement therapy for these patients. The survival benefit of kidney transplantation over dialysis is observed even when using kidneys from donors with characteristics that shorten long-term kidney graft survival.[91]

The duration of dialysis and timing of transplantation is also of great importance. Pre-emptive kidney transplantation is associated with the best results in all patients with kidney failure and diabetic patients in particular.[92,93] There is a significant increase in the relative risk for patient death or graft loss (death-censored) with increasing time of pre-transplantation dialysis.[90,92]

A recent report has examined the association between pancreas transplantation and survival in patients with diabetes.[94] Using data from the UNOS/OPTN, Venstrom and colleagues performed a retrospective cohort study of all case mortality within four years of transplantation for recipients of SPK transplants, PAK transplants, and PTA, and compared to the mortality of patients who remained on the waiting list for the same type of transplant. (Table 5) All transplant recipients experienced a higher risk of mortality early after the transplant procedure. Four years after transplantation, recipients of a SPK transplant had a 57% lower cumulative risk of mortality than patients who remained on the waiting list for a SPK transplant. The four year cumulative risk of mortality was 42% higher for recipients of a PAK transplant than for PAK candidates remaining on the waiting list. The four year cumulative

Relative Risk of Death After Transplantation
(Reference: Wait-Listed Patients)

Time After Transplant	0 – 90 days	4 years (cumulative)
SPK	1.52	0.43*
PAK	2.89	1.42*
PTA	2.27	1.57

(Data from Venstrom et al., JAMA 289:2817, 2003)

Table 5

mortality risk was 57% higher for recipients of a PTA than for PTA candidates remaining on the waiting list.

A possible explanation for the lack of benefit with solitary pancreas transplantation as noted in the above study is that advances in the care of diabetic patients may have reduced their mortality, making the risks of surgery and immunosuppression more significant.[94,95] The report shows a survival benefit of SPK transplantation for patients with diabetes and kidney failure.[94] The higher mortality of SPK candidates while on dialysis (as compared to the mortality of patients waiting for solitary pancreas transplantation) is a likely explanation for the differences observed on the impact of pancreas transplantation upon patient survival for SPK transplant, PAK transplant, and PTA recipients.

Given the major impact of kidney transplantation on the survival of diabetic patients with kidney failure, it has been more difficult to determine the relative effect of SPK transplantation as compared to KTA on patient survival. Patients undergoing SPK transplantation experience higher morbidity early after transplantation than patients undergoing KTA. Rejection episodes, infections, surgical complications, and readmissions occur more often in recipients of SPK transplants.[96-98] Early reports had raised concerns about excess mortality associated with pancreas-kidney transplantation.[99] Although comparisons are limited in many cases because of the selection of healthier patients for SPK transplantation, recent reports have revealed encouraging results.

The Transplant Group at the University of Wisconsin reported on the impact of transplantation on annual mortality rates and the observed/expected life span (ratio of length of patient survival after transplantation compared with average life span of an age-matched healthy individual from the same population) for transplant recipients.[100] SPK transplantation significantly reduced annual mortality rates compared to LDK transplantation and DDK transplantation for diabetic transplant recipients. The observed/expected life span for SPK transplant recipients was similar to that of non-diabetic transplant recipients and higher than for diabetic KTA recipients.

The Transplant Group at the Karolinska Institute in Sweden compared mortality rates in a group of 14 patients with SPK transplants with a group of 15 diabetic patients who had also undergone SPK transplantation but who had lost the pancreas during the first year post-transplantation or who were eligible for SPK transplantation but ultimately elected for KTA.[101] The mortality rate at ten years was 20% for SPK transplant recipients and 80% for patients who only had a functioning kidney transplant. Similarly, in a review of the UNOS database, SPK recipients with a functioning pancreas had higher survival than SPK recipients who had experienced pancreas graft loss.[102]

Using data from the USRDS and the U.S. Scientific Renal Transplant Registry, Ojo and colleagues examined survival of a total of 13,467 patients with diabetes and onset of kidney failure before the age of 40 (presumed to represent nephropathy from type 1 diabetes) who were enrolled in the waiting list for kidney or pancreas-kidney transplantation between October 1988 and June 1997.[53] Adjusted ten year survival was 67% for SPK transplant recipients, 65% for LDK transplant recipients, and 46% for DDK transplant recipients. There was an initial risk of higher mortality associated with SPK, but by five years after transplantation the relative risk of death (using wait-listed patients on dialysis as reference) was 0.40 for SPK transplant recipients, 0.45 for LDK transplant recipients, and 0.75 for DDK transplant recipients. The expected remaining years of life were 23.4 after SPK transplantation, 20.9 after LDK transplantation, 12.6 after DDK transplantation, and 8 years for wait-listed dialysis patients. Longer duration of

Pretransplant Dialysis and Mortality

Pretransplant duration of dialysis	Mortality risk
Preemptive transplant	1.0
0 – 6 months	1.40
7 – 12 months	1.58
13 – 24 months	1.59
>24 months	1.75

(Data from Ojo et al., *Transplantation* 71:82, 2001)

Table 6

Effect of Pancreas Transplant on Mortality with Kidney Failure

Location	Primary intention to-treat modality	Mortality risk
Non-Leiden	Kidney transplant	1
Leiden	Pancreas-kidney transplant	0.53
Leiden	(Transplanted patients)	0.32

(Data from Smets et al., *Lancet* 353:1915, 1999)

Table 7

dialysis while waiting for a kidney/pancreas transplant was associated with a progressive increase in mortality risk.[53] (Table 6)

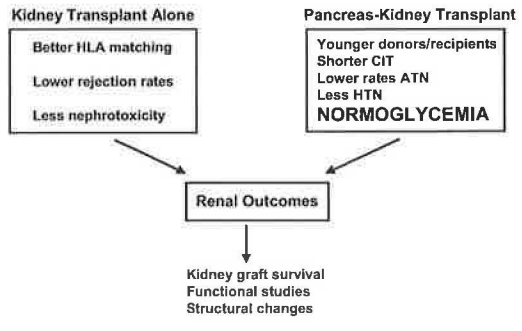
There are no randomized controlled trials of SPK transplantation vs KTA in diabetic patients with kidney failure, but the report of Smets and colleagues is especially relevant.[103] In a population based study, the Transplant Group at Leiden University in the Netherlands compared mortality for diabetic patients after initiation of renal replacement therapy in two areas of the Netherlands that differed in that SPK transplantation was the primary intention to treat modality for kidney failure in diabetic patients in one area compared to KTA in the second area. (Table 7) The hazard ratio for mortality after starting renal replacement therapy was 0.53 in the area where SPK transplantation was the primary intention to treat modality compared to the area where KTA was the predominant type of treatment. Mortality rates on dialysis and ability to maintain kidney graft function after transplantation were the same in both areas.

Although none of the above studies can prove a causal relationship between SPK and improved survival, patients who undergo SPK experience better survival than those undergoing KTA.[53] Differences in patient selection, pre-transplant evaluation, and post-transplantation care may influence outcomes. Donor and recipient factors are usually more favorable for SPK transplant recipients.[104,105]

Microvascular Disease

Nephropathy

Pancreas Transplantation and the Kidney



(Information partly adapted from Hricik, *Sem Nephrol* 20:168, 2000)

Figure 9

A potential benefit of a functioning pancreas transplant is the protection of the kidney allograft from recurrent diabetic nephropathy. Comparison of renal outcomes between recipients of SPK transplants and KTA are complicated by differences in multiple factors known to affect kidney transplant results. (Figure 9) Patients undergoing SPK transplantation are usually younger and receive kidneys from younger donors and have shorter cold ischemia times, lower rates of delayed graft function, and lower prevalence of hypertension (especially with bladder drainage of pancreas). On the other hand, SPK transplant

recipients experience higher rates of acute rejection, receive grafts with higher rates of HLA mismatching, and are exposed to higher doses of nephrotoxic immunosuppressive drugs.[13,14,97,104,106,107]

Important renal outcomes after pancreas transplantation include kidney graft survival, renal functional studies, and histologic evaluation of the kidney. As previously noted, one year kidney graft survival rates are excellent for recipients of KTA or SPK transplants. Acute rejection episodes have a negative impact on long-term kidney graft survival for recipients of SPK transplants and KTA. Patients with acute rejection episodes affecting both the kidney and the pancreas allografts have the worst long-term kidney graft survival.[108] Chronic allograft nephropathy is present in a large proportion of long-term recipients of SPK transplants.[109] Recipients of kidneys from HLA identical siblings have the lowest rate of acute rejection and delayed graft function, lowest creatinine at discharge, and need lower doses of immunosuppressive drugs, and therefore show the best kidney graft survival rates at one and five years after transplantation.[98]

Recently, the group at the University of Wisconsin has reviewed factors associated with kidney graft survival in a cohort of 430 SPK recipients.[110] Forty percent of patients developed impaired glycemia or frank diabetes. Development of impaired glycemia and especially diabetes were strongly associated with a significantly higher risk of kidney graft loss. Poor glycemic control might have been responsible for the worse kidney graft outcomes in patients with impaired glycemia and diabetes, although rejection, differences in immunosuppressive drugs, and nephrotoxicity, among others, may have also influenced the observations.

Single center studies of kidney function after SPK transplantation have revealed variable results. Some centers have reported no differences in kidney function, while others have noted a positive or negative impact in kidney function for SPK transplantation as compared to KTA.[111-114] SPK recipients who lose their pancreas allograft during the first year after transplantation have significant increases in urine albumin excretion at ten years compared to SPK recipients with a functioning pancreas transplant.[115]

Structural studies have provided valuable insights into the role of pancreas transplantation and glucose control in kidney disease. In diabetic nephropathy, there is accumulation of extracellular matrix in the mesangium, glomerular basement membrane (GBM), tubular basement membrane (TBM), and interstitium.[116,117] Mesangial expansion caused by mesangial matrix accumulation as well as hyalinosis of glomerular arterioles and global glomerular sclerosis, occur in association with decreases in filtration fraction, and declining glomerular filtration rate.

Mesangial and GBM lesions of diabetic nephropathy develop in kidneys from non-diabetic living donors or deceased donors by two years after transplantation into diabetic recipients.[118] The relationship between hyperglycemia and diabetic lesions in kidney transplant recipients is illustrated by the development of significantly higher increases in mesangial matrix by five years after transplantation in diabetic recipients treated with a standard insulin therapy as compared to patients treated with an intensive insulin regimen.[119] Transplantation of the pancreas prevents the development of histologic changes of diabetic nephropathy in recipients of SPK transplants and the progression of histologic changes of diabetic nephropathy in recipients of PAK transplants.[120,121]

Some very interesting findings have been reported in a group of patients with type 1 diabetes and mild to advanced lesions of diabetic nephropathy, but without uremia, and who

Pancreas Transplantation and Diabetic Nephropathy
(follow up 10 years)

Time	Baseline	5 years	10 years
Functional studies			
UAE (mg/day)	103	30	20
Creat. Clearance (cc/min)	108	74	74
Structural studies			
GBM thickness (nm)	594	570	404
Mesangial fractional volume/glomerulus	.033	.039	.027

Table 8

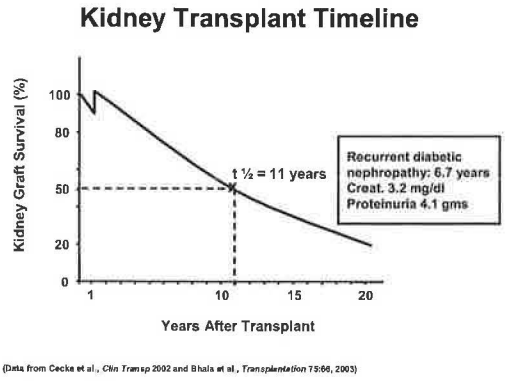


Figure 10

underwent pancreas transplantation alone (PTA) at the University of Minnesota.[122] Studies of kidney function and kidney biopsies were performed at baseline and five and ten years after PTA. (Table 8) Creatinine clearance decreased from baseline to five years, but then remained stable. Urine albumin excretion decreased from abnormal at baseline to normal at five and ten years. Histological lesions, including abnormal thickness of the GBM and TBM, as well as increased mesangial matrix and mesangial matrix fractional volume, persisted or increased by five years. Nevertheless, ten years after PTA (and normoglycemia), the thickness of the GBM and TBM and increased mesangial matrix decreased to normal, and the nodular lesions of Kimmelstiel-Wilson disappeared.

The beneficial effects of pancreas transplantation in preventing diabetic nephropathy after kidney transplantation may become more clinically important as advances in immunosuppression lead to reductions in kidney graft loss from rejection. Recurrent diabetic nephropathy has been recently noted to have a more accelerated course than previously reported, making the potential benefits of pancreas transplantation even more relevant.[116] (Figure 10)

Retinopathy

Many patients with diabetes and kidney failure have advanced retinopathy and even blindness at the time of presentation for SPK transplantation.[123-125] As many of these patients have received photocoagulation or vitrectomies prior to transplantation, elucidating the effects of pancreas transplantation on the progression of retinopathy has been difficult. Recent reports have noted that SPK transplant recipients have higher rates of stabilization of diabetic retinopathy following transplantation.[124,125]

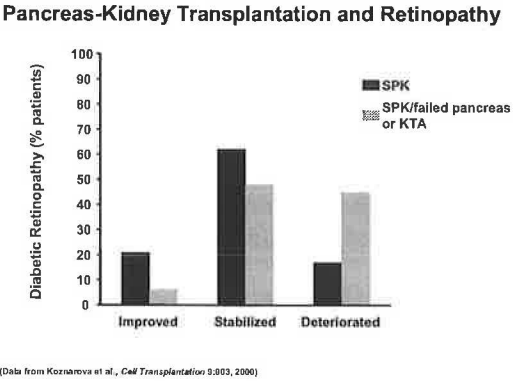


Figure 11

In a prospective study, SPK transplant recipients with functioning pancreas had higher rates of improvement or stabilization of fundoscopic findings of diabetic retinopathy and lower rates of deterioration than recipients of a kidney transplant alone or SPK with failed pancreas.[125] (Figure 11) The need for additional laser therapy was also much lower in the group with the functioning pancreas transplant.[125]

Diabetic microangiopathy in the conjuctival microcirculation improves by 18 months after transplantation in SPK transplant recipients, but not in diabetic recipients of KTA.[126] The prevalence of cataracts of all types increases after transplantation.[123,124,127]

Neuropathy

Diabetic neuropathy is characterized by progressive axonal loss manifested by diffuse somatic and autonomic abnormalities.[128] Successful pancreas transplantation halts the progression of diabetic polyneuropathy in recipients of SPK, PAK, and KTA.[128,129] A long-term study (with ten years of follow up) from the University of Minnesota has shown that restoration of normoglycemia with a pancreas transplant is associated with partial improvements in clinical examination scores and neurophysiological testing in pre-existing abnormalities in motor and sensory nerve conduction as well as autonomic function.[128] Improvements in diabetic autonomic neuropathy after pancreas and kidney transplantation occur in both vasomotor functions that reflect sympathetic adrenergic responses and cardiac tests that measure vagal cholinergic responses.[130] Improvements in cardiac autonomic measures such as heart rate variability are particularly significant within the first year after SPK transplantation.[131]

The improvements in nerve action potentials after successful SPK transplantation are gradual and sustained and consistent with axonal regeneration and partial reversal of diabetic neuropathy.[132] Nevertheless, changes toward normalization are mild, probably due to previous structural damage to the peripheral nerves.[128] Deterioration of neurophysiological studies after failure of pancreas transplantation in SPK recipients underscores the importance of metabolic control in the changes observed in diabetic neuropathy.[133]

Macrovascular disease

Kidney transplant candidates with diabetes have a high incidence of atherosclerotic vascular disease, and close to one-third of patients suffer a major vascular event (myocardial infarction, stroke, or amputation) within three years after the initial pre-transplant evaluation.[134] Cardiac-vascular disease is the most important cause of morbidity and mortality in diabetic transplant recipients.[26,134]

Earlier studies comparing recipients of SPK transplants and KTA had not shown benefits for pancreas transplantation in halting the progression of coronary artery disease, cerebrovascular disease, or peripheral vascular complications.[135,136] More recent studies, however, have been more encouraging. Recipients of successful SPK transplants have better blood pressure control and left ventricular ejection fraction.[137,138] Moreover, type 1 diabetic patients with functioning kidney and pancreas transplants have lower atherosclerotic risk profiles, reductions of intimal media thickening, and normal endothelial function when compared to type 1 diabetics receiving KTA.[139]

The group at Leiden University in the Netherlands recently reported a prospective observational angiographic study in 32 type 1 diabetic patients who underwent SPK transplants.[140] Patients were divided into two groups based on whether the pancreas allograft was functioning (non-function defined as need to reinstitute insulin therapy). All patients underwent coronary angiography prior to transplantation and a mean of 3.9 years after transplantation. (Table 9) The observed progression of coronary atherosclerosis was on average almost double

SPK Transplantation and Coronary Atherosclerosis
(n=32 patients, follow up 3.9 years)

Transplant (SPK)	Functioning pancreas n=26	Pancreas loss n=6
Mean segment diameter loss (mm/yr)	0.024	0.044
Minimum obstruction diameter loss (mm/yr)	0.037	0.061
Regression atherosclerosis (patients)	38%	0%

(Data from Jukema et al., Diabetes Care 25:906, 2002)

Table 9

for patients in whom the pancreas graft had failed compared to those patients with a functioning pancreas, although the differences did not reach a statistical significance. Among the patients with a functioning pancreas graft, 38% had regression of coronary atherosclerosis compared to none for patients who experienced pancreas loss for a statistically significant difference. This study is the first one to show a benefit for a functioning pancreas transplant on the progression of coronary atherosclerosis in SPK transplant recipients.

Quality Of Life

A principal goal of transplantation is improving quality of life. Many studies have examined the impact of transplantation upon quality of life, and most have reported a beneficial effect of pancreas and kidney transplantation.[141-144] Patients with successful pancreas and kidney transplants also report higher quality of life than those pancreas and kidney transplant recipients who experience loss of the pancreas after transplantation.[145]

A prospective observational study has provided valuable information on the impact of SPK transplantation as compared to KTA on quality of life issues.[146] After three years of follow up, most measures of health status and quality of life improved for both transplant groups. SPK transplant recipients reported greater improvements than KTA recipients in physical health and in diabetes-specific areas of quality of life, including satisfaction with health and therapy. Recipients of KTA reported fewer emotional problems with role activities by three years post-transplantation. The study could not determine if higher expectations from SPK patients (which were significantly more likely to be working one year post-transplantation) could have influenced the emotional scores. Health-related quality of life measures for diabetic recipients of SPK transplants or KTA did remain below that of the age-matched population.

CONCLUSION

Kidney failure and diabetes are two chronic medical conditions that shorten lives and lead to multiple complications which reduce the quality of life of many patients. The incidence and prevalence of kidney failure and diabetes continue to increase yearly. Diabetic patients are disproportionately at risk for kidney failure and diabetes has become the most important cause of kidney failure.

Kidney transplantation improves survival for patients with kidney failure and is the best form of renal replacement therapy for most patients, including those with diabetes. Kidney transplantation should be performed as early as possible in the course of treatment for kidney failure. Pancreas transplantation is currently the most reliable therapy to restore insulin-independence and normoglycemia to diabetics. Recipients of simultaneous pancreas and kidney transplants have a higher survival rate than those patients waiting for a transplant. Pancreas transplantation has beneficial effects in preventing diabetic nephropathy and in the course of retinopathy and neuropathy. Pancreas transplantation also appears to have a beneficial effect on some forms of diabetic macrovascular disease.

Advances in surgical techniques, immunosuppression, and medical care of transplant recipients have made it possible for recipients of kidney and pancreas transplants to accomplish two very important objectives: restoration of kidney function and achievement of sustained normoglycemia. From the perspective of patients with kidney failure and diabetes, kidney and pancreas transplantation can also achieve some other major objectives. Elimination of hyperglycemia and hypoglycemia, discontinuation of the need for constant monitoring of glucose levels and multiple daily adjustments in insulin therapy, liberalization of strict dietary and fluid restrictions, and freedom from dialysis are proven benefits which can improve the quality of life of all patients with successful pancreas and kidney transplants.

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