KIDNEY AND PANCREAS TRANSPLANTATION

FOR THE DIABETIC PATIENT

WITH RENAL FAILURE

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END STAGE RENAL DISEASE AND DIABETES

The number of individuals affected by renal disease continues to increase steadily in the United States and most other countries around the world [1]. Based on data from the 3rd National Health and Nutrition Examination Survey (NHANES III), it is estimated that among the U.S. non-institutionalized population 10.9 million people have creatinine values of 1.5 mg/dl or greater [2]. According to the USRDS registry, the incidence of new cases of ESRD in the U.S. continues increasing at about 7% per year. The number of patients receiving treatment for ESRD now exceeds 300,000 in the U.S. [1]

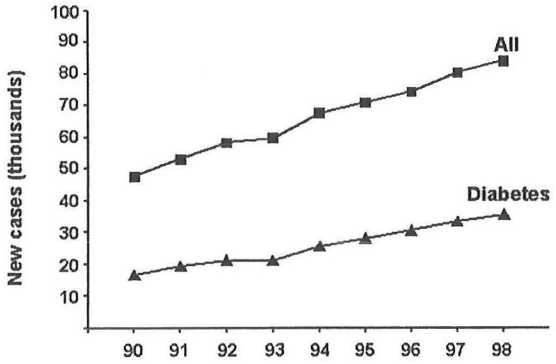

Figure 1: Incidence of Reported ESRD (Adapted from USRDS, ADR 2000)

Diabetes is the leading cause of ESRD in the United States and has become increasingly important in most other industrialized nations. [1,3,4,5] The incidence of new cases of ESRD from diabetes in the U.S. (adjusted for age, gender and race) continues to increase at about nine percent per year. Diabetes is now responsible for close to half of all new cases of ESRD. [1] (See Figure 1.) Reasons for the increased incidence of diabetic ESRD include the rise of diabetes in the general population, better survival of diabetic patients from non-renal complications and increased referrals of diabetic patients for renal replacement therapy. [1,4]

Diabetic patients with ESRD suffer from 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 ESRD. [6,7] Diabetic patients with ESRD have more hospital admissions and hospital days per year than non-diabetic patients. [1]

Patients with ESRD from diabetes have higher mortality rates from multiple causes including cardiac and cerebrovascular disease, sepsis and withdrawal from dialysis compared to non-diabetic patients [6,7]. Poor nutrition and suboptimal dialysis have been noted to be important factors in the lower survival of diabetics on dialysis. [8,9]. On a positive note, improvements in the care of diabetic ESRD patients have led to reductions in mortality rates in the last few years. [1,4]

RENAL REPLACEMENT THERAPY FOR THE DIABETIC PATIENT

Dialysis and renal transplantation are therapeutic options which can prolong life and offer substantial rehabilitation for diabetic patients with renal failure. More than 3/4 of all diabetic patients with ESRD receive dialysis as their form of renal replacement therapy. [1] (See Figure 2.).

Historically, patient and graft survival rates for diabetic renal transplant recipients have been lower than for non-diabetic patients. [10,11,12,7] Nevertheless, recent reports have noted excellent patient and

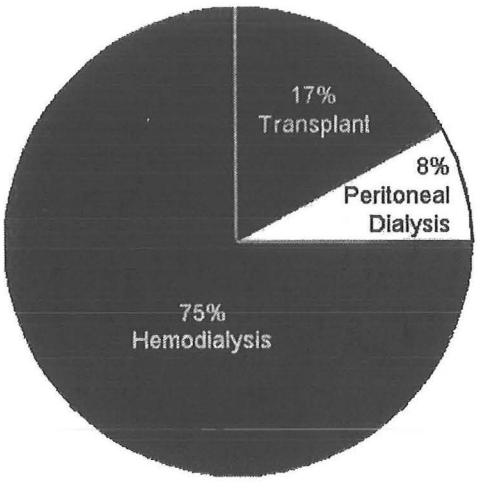

Figure 2: Renal Replacement Therapy for Diabetes
(Data from USRDS ADR 2000)

graft survival rates for diabetic renal transplant recipients and which are now similar, at least short-term, to those seen in non-diabetic renal transplant recipients. [13] Long-term, however, death with graft function is more common for diabetic patients than for patients with ESRD from other causes [14].

Diabetes has now become the leading disease among renal transplant recipients. [13]. Most studies comparing the survival for patients treated for ESRD with dialysis or renal 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. [6]. Using data from the 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 cadaveric renal transplant with that of patients on dialysis on the waiting list for renal transplantation. [15]. 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. The patients undergoing renal transplantation had a higher mortality rate early after transplantation (related to surgery and high intensity immunosuppression). By 18 months after transplantation however, recipients of a renal transplant had a mortality risk estimated to be 68% lower than that for the patients on the waiting list. The projected increase in life span conferred by transplantation was 10 years. [15]. Diabetic patients had a 73% reduction in their mortality risk by 18 months after transplantation compared to those diabetic patients remaining on the waiting list. The projected increase in life span for all diabetic patients was 11 years and for young diabetics (20-39 years of age) was 17 years. [15]. (See Figure 3.)

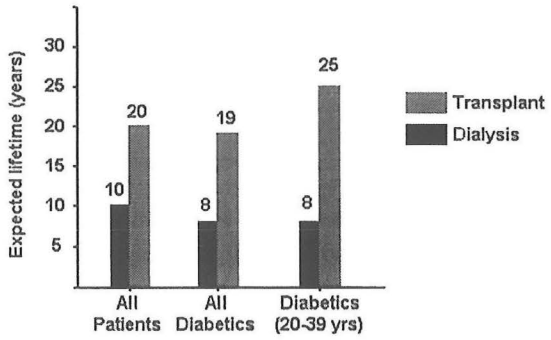

Figure 3: Projected Years of Life with ESRD Effect of Transplantation
(Adapted from Wolfe et al., *NEJM* 341:1725, 1999)

Although in the absence of a randomized trial it is difficult to establish causation between renal transplantation and superior survival for diabetic patients with ESRD, it is unlikely that such a study will ever be conducted [16]. The observations of the great benefit of transplantation upon survival for diabetic patients with renal failure makes transplantation the preferred therapy for these patients. Moreover, for all patients with ESRD, and diabetic patients in particular, preemptive transplantation is associated with the best results. There is a significant increase in the relative risk for patient death or graft loss (death-censored) with increasing time of pre-transplantation dialysis. [17,18].

A functioning renal transplant permits superior rehabilitation than dialysis for diabetic patients with ESRD [7]. Patients with diabetes and renal failure report better health and quality of life after transplantation [19].

PANCREAS TRANSPLANTATION

Current Options and Outcomes

Intensive therapy with insulin delays the onset and slows the progression of diabetic nephropathy, retinopathy, and neuropathy in patients with type I diabetes [20,21]. The beneficial effects of insulin therapy in preventing diabetic complications occur in association with improved glycemic control [20]. Successful pancreas and islet transplantation are currently the only therapies that can reliably achieve normoglycemia by reestablishing endogenous insulin secretion responsive to normal feedback regulation [22,23,24,25,26]. Pancreatic allograft transplantation is an accepted form of treatment for patients with type I diabetes who require renal replacement therapy [27,28]. Recent progress in the field of islet transplantation may soon lead to its progressive introduction into clinical medicine.

A successful pancreas transplant improves quality of life by reestablishing insulin independence and reducing or eliminating hypoglycemic episodes [27,24,25]. There are several options regarding transplantation of the pancreas in a diabetic patient [22,27,29]. (See Table 1.) In simultaneous pancreas/kidney transplantation (SPK) the pancreas transplant is performed at the same time as the kidney transplant in diabetic patients with renal failure. Only one surgical procedure is required and immunosuppression is used to prevent both pancreas and kidney allograft rejection.

Pancreas Transplantation
1. Simultaneous Pancreas Kidney (SPK)
2. Pancreas After Kidney (PAK)
3. Pancreas Transplant Alone (PTA)
4. Simultaneous Pancreas-Living Kidney (SP-LK)
5. Simultaneous Pancreas Kidney- Living Donor (SPK-LD)

Table 1

Pancreas after kidney transplantation (PAK) is performed in diabetic patients who have previously undergone renal transplantation. Advantages include the excellent short and long-term kidney graft survival associated with living donor transplantation (in those patients with a living kidney donor), shorter time or avoidance of dialysis and potentially shorter waiting times for the pancreas transplant [29,30]. The main disadvantage is that it involves a second surgical procedure.

Pancreas transplantation alone (PTA) is solitary transplantation of the pancreas and is used in individuals who have not suffered from end organ damage from diabetes and can potentially benefit from prevention of future diabetic complications [29,31]. The main concerns for this group of patients relate to the risk of surgery and post transplant 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 management to prevent acute complications [22,27].

Recently, simultaneous cadaver-donor pancreas and living-donor kidney (SPLK) has been introduced as another option [32]. The main advantages include shorter waiting times and decreased rates of renal

delayed function (with a potential for better short and long-term survival of the renal graft) and expansion of the organ donor pool.

Finally, simultaneous pancreas/kidney transplant from living donors (SPK-LD) using one kidney and segment of the pancreas from one living donor is another option [33,34]. Potential advantages include better matching, lower risks of rejection and elimination of waiting time [33]. The main disadvantage is the risk of hemipancreatectomy for the donor. This procedure is uncommon.

Data from UNOS and the International Pancreas Transplant Registry (IPTR) show that the total number of pancreas transplants continues to increase each year [35,36] (Figure 4). The majority of transplants are SPK but the proportion of PAK has increased significantly to more than 10% per year. PTA constitute about 4-5 % of all pancreatic transplants per year [36].

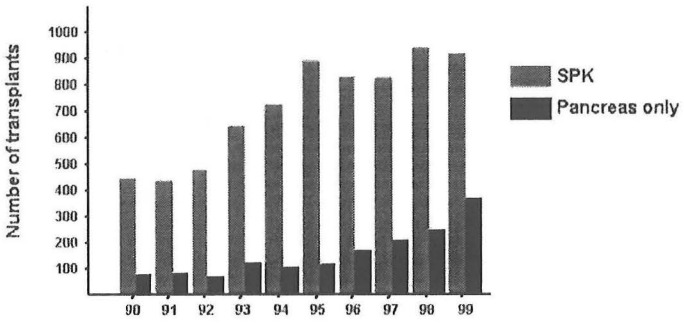

Figure 4: Annual Number of Pancreas Transplants (Adapted from UNOS, Annual Report 2000)

The first pancreas transplant was performed in The University of Minnesota in 1966 [37]. 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 3 decades [23,38,39,40].

Many excellent reviews describe the technical aspects of renal transplantation [41,22,40]. The pancreas allograft with the small portion of duodenum from the donor is usually placed intraperitoneally in the right iliac fossa.

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 mesenteric artery. 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 [41].

Venous drainage is usually from the portal vein of the pancreatic allograft end-to-side to the external iliac vein of the recipient [41]. This systemic venous drainage of the pancreas is associated with hyperinsulinemia as insulin bypasses degradation by the liver [23].

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 [38,40]. Enteric drainage modalities were associated with high rates of anastomotic leaks, abscess formation and sepsis [42,40].

The introduction of bladder drainage of the exocrine pancreas was a major step in the progress of pancreas transplantation in the 1980's [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 [40,42]. 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 a non-anion gap metabolic acidosis [43,44,45].

Urologic complications occur from prolonged exposure to pancreatic enzymes and persistently alkaline urine and include urinary tract infections, hematuria, duodenitis, (calcium) bladder stones, cystitis, urethritis, reflux pancreatitis, and urine leaks [26,46,47,48]. Chronic complications of bladder drainage lead to conversion from bladder drainage to enteric drainage in close to 10% of cases during the first year and more than 20% on long term follow-up [36,40,47].

Enteric drainage 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, the development of better immunosuppression has lead to reductions in the rates of acute rejection of the pancreas [40]. Second, the use of pancreatic allograft biopsies makes it possible to reliably diagnosis rejection even when urinary amylase cannot be monitored with enteric drainage [49,50,51,52].

In enteric drainage, the pancreas allograft with a segment of donor duodenum is anastomosed side-to-side to the recipient's small bowel (usually ileum) [41]. In some cases the donor duodenum is anastomosed distally end-to-end to a diverting Roux-en-Y limb of recipient jejunum [45,53]. 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 [45,53]. Patients with PE drainage do not have the levels of hyperinsulinemia seen in patients with systemic venous drainage [44].

Although uncommon until the mid 1990's, enteric drainage is now the most common method for drainage of the exocrine pancreas [36]. Portal enteric drainage is used in about 20% of cases with enteric drainage [36]. Short- term results of pancreatic transplantation using bladder drainage, enteric drainage and portal enteric drainage of the pancreas are similar [45,53,54,55].

The outcomes of pancreas transplantation have 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 [36]. (See Figure 5.) For patients with pancreatic transplants that function at one year very few lose their grafts each succeeding year [56].

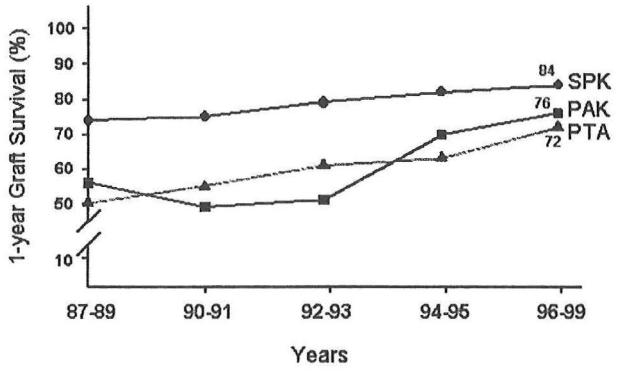

Figure 5: Pancreas Graft Survival
(Data from IPTR, *Clin Transp* 1999)

The majority of pancreas transplant recipients are reported as having type I diabetes, but nearly 4% have type II diabetes [36]. Short-term outcomes appear to be similar for patients with type I and type II diabetes [36,57,43].

Causes of Pancreas Graft Loss

Pancreas graft failure can occur because of technical/surgical complications, rejection, patient's death with a functioning transplant, recurrence of autoimmune diabetes or development of type II diabetes [40,36,58].

Technical failures/surgical complications

Pancreas transplantation has the highest surgical complication rate of all routinely performed organ transplantations [59,60]. Technical failures are the most common causes of pancreas graft losses although rates have declined to less than 10% in the current era [36]. The most common reasons for technical failures are graft thrombosis, infection, pancreatitis and bleeding [36]. The incidence of these complications was highest for pancreas 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 [36,60]. 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 [36,61,62].

Rejection

Acute rejection is a serious complication of transplantation and in some series the most important cause of pancreas graft loss, short and long-term [40,63]. 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, 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 [64,65,66,67,68]. The percentage of graft losses due to acute rejection (censored for death with graft function) is as low as 2% for recipients of SPK, 7% for recipients of PAK and 9% for recipients of PTA [36]. PE drainage of the pancreas has been associated with fewer rejection episodes suggesting a possible immunological advantage for this form of venous drainage with delivery of donor antigen to the liver via the portal circulation [45,69].

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 [63,26,70,71].

Monitoring of urinary amylase is useful in the diagnosis of rejection in pancreas recipients with bladder drainage [42]. Early diagnosis of rejection in all pancreas recipients, and especially recipients of PAK or PTA, is facilitated by the use of pancreatic allograft biopsies [49,50,51,52]. Multiple other methods to diagnose pancreatic rejection have been proposed including monitoring of serum amylase and lipase, insulin release after IV glucose/glucagon and MRI imaging, but they lack optimal sensitivity and specificity [26,72]. Hyperglycemia is usually a late event in pancreas rejection as the exocrine pancreas and acinar cells are the initial targets in pancreas rejection [73,74].

Death with a functioning graft

Patient survival at one year now exceeds 95% for recipients of pancreas transplants [36]. Nevertheless, death with a functioning graft is still one of the most important causes of pancreas graft loss especially after the early period [40,75]. Cardiac disease is the most common cause of deaths at all times after transplantation [76]. Many patients present with sudden death [75]. Deaths from infection tend to occur more often in the early period after transplantation [76,75].

The most important factors predicting high mortality after pancreas/transplantation are older recipient age (older than 45), longer time on dialysis waiting for transplantation and failure of the renal allograft [36,75,76].

Recurrence of autoimmune diabetes

Type I diabetes is an autoimmune disorder in which the beta cells that produce insulin are selectively destroyed [77]. Type I diabetes has recurred in the setting of pancreas transplants between identical twins when no immunosuppression was used [23,78]. Although uncommon, recurrent autoimmune diabetes has also been reported in recipients of cadaveric pancreas transplant [79]. 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). At the same time there was histologic evidence of insulitis with selective destruction of beta cells and preservation of alpha and delta cells [36]. A recent study examined antibody reactivity (by measuring antibodies against glutamic acid decarboxylase and protein tyrosine phosphatase IA-2A) in recipients of pancreas allografts [80]. 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 [80]. The pattern of islet antibody reactivity was characteristic of that found in preclinical type I diabetes and suggested a role of recurrent autoimmunity in the failure of the pancreas allograft [80].

Development of type II diabetes

Type II diabetes can be the cause of hyperglycemia after pancreas transplantation [81]. Recipients of SPK have reduced insulin secretory capacity and evidence of insulin resistance [82]. Glucose homeostasis is obtained with increased proinsulin secretion and increased insulin secretion rates [83]. 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 resistence to insulin, denervation of the pancreas allograft and decreased renal clearance of insulin in some patients [25,83]. In addition to contributing to peripheral insulin resistence, high doses of immunosuppressive drugs such as cyclosporine, tacrolimus and steroids can be associated with structural damage to beta cells [84].

Recognition of type II diabetes after pancreas transplantation is particularly important as cell damage and hyperglycemia may be reversible (at least in the early stages) [84].

Metabolic Control

A functioning pancreas transplant results in independence from insulin [22]. 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 [85,86,87]. (See Table 2.) Hyperinsulinemia is present in pancreas transplant recipients (especially with systemic venous drainage of the pancreas). C-peptide levels (which may have some biological activity in controlling glucose control) are similar to normal controls [85,88].

Pancreas Transplantion and Metabolic Control

Time after Transplant	1 year	5 years
FPG (mg/dl)	85	88
HbA1c (%)	5.3	5.2
Acute insulin response (to glucose, uV/ml)	135	116
Acute C-peptide response (to glucose, nmol/L)	1.13	1.30
Acute glucagon response (to arginine, pg/ml)	292	281

Table 2: Adapted from Robertson et al., *J Investig Med* 44:549, 1996)

Hypoglycemia may occur after pancreas transplantation but it is usually mild and of limited clinical impact [89,90]. Glucose counterregulation is abnormal in patients with long standing diabetes. Pancreas transplantation restores hypoglycemia-induced glucagon secretion and hepatic glucose production [91]. Epinephrine responses and symptom recognition to hypoglycemia also improve after pancreas transplantation [92].

Pancreas transplantation improves the lipid profiles with higher HDL-cholesterol and significantly lower triglycerides and cholesterol/HDL cholesterol levels, noted early after transplantation [93]. Nevertheless, elevated insulin levels, lipoprotein lipase and cholesteryl ester are present in these patients [94].

POTENTIAL BENEFITS OF PANCREAS (AND KIDNEY) TRANSPLANTATION

Patient Survival

Patients undergoing SPK transplantation experience higher morbidity early after transplantation than patients undergoing kidney transplantation alone. Rejection episodes, infections, surgical complications and readmissions occur more often in recipients of combined pancreas/kidney transplants [95,96,97]. Early reports had raised concerns about excess mortality associated with pancreas/kidney transplantation [98]. Although comparisons are limited in many cases because of the selection of healthier patients for combined kidney pancreas transplantation, recent reports have revealed some very encouraging results.

The transplant group at The University of Wisconsin has reported 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 [99]. SPK transplantation significantly reduced annual mortality rates compared to living-donor kidney transplantation and cadaveric renal 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 kidney transplant alone recipients [99].

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 with a functioning kidney transplant alone (pancreas lost during the first year due to a technical complication in 9 patients, rejection in 1 patient or eligible patients for SPK that elected kidney transplant alone, 5 patients). The mortality rate at 10 years was 20% for SPK transplant recipients and 80% for patients with a kidney transplant alone.

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 pancreas/kidney transplantation was the primary intention to treat modality for ESRD in diabetic patients in one area compared to kidney transplantation alone in the second area [100]. The hazard ratio for mortality after starting renal replacement therapy was 0.53 in the area where pancreas/kidney transplantation was the primary intention to treat modality compared to the area where kidney transplantation alone was the predominant type of treatment.

Recently, Ojo and colleagues used data from the USRDS and U.S. Scientific Renal Transplant Registry to examine survival of a total of 13,467 patients with diabetes and onset of ESRD before the age of 40 (presumed to represent nephropathy from type I diabetes) who were enrolled in the waiting list for kidney or pancreas/kidney transplantation between Oct. 1988 and June 1997 [76]. Adjusted 10 year survival was 67% for SPK transplant recipients, 65% for living-donor kidney transplant recipients, and 46% for cadaveric renal transplant recipients ($P<0.001$). There was an initial risk of higher mortality associated with pancreas/kidney transplantation, but by 5 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 living kidney donor transplant recipients, and 0.75 for cadaveric renal transplant recipients. The expected remaining years of life were 23.4 after simultaneous pancreas/kidney transplantation, 20.9 after living kidney donor transplantation and 12.6 after cadaveric renal transplantation and 8 years for wait-listed dialysis patients. (See Figure 6.)

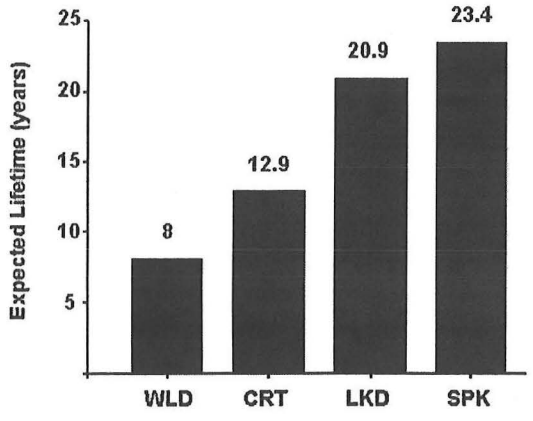

Figure 6: Projected Extra Lifetime (years) with Transplantation or Kidney or Pancreas-Kidney (Adapted from Ojo et al., *Transp* 71:82, 2001)

Although none of the above studies can prove a causal relationship between simultaneous pancreas/kidney transplantation and improved survival, it is clear that patients who undergo pancreas/kidney transplantation have better survival than those undergoing kidney transplantation alone [76]. Differences in patient selection, pre-transplant evaluation and post transplantation care may have also influenced the outcomes.

Renal Graft Outcomes

More than one-half of diabetic patients undergoing transplantation now receive kidney/pancreas transplants [13]. A potential benefit of a functioning

pancreas is protection of the renal allograft from recurrent diabetic nephropathy. Comparisons of renal outcomes between recipients of SPK transplants and kidney transplants alone (KTA) recipients are complicated by differences in multiple factors known to affect kidney transplant results. Patients undergoing SPK usually receive kidneys from younger donors and have shorter cold ischemia times, lower rates of delayed graft function and lower prevalence of hypertension (for 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 [26,101,102,96,95,103]. (See Figure 7.)

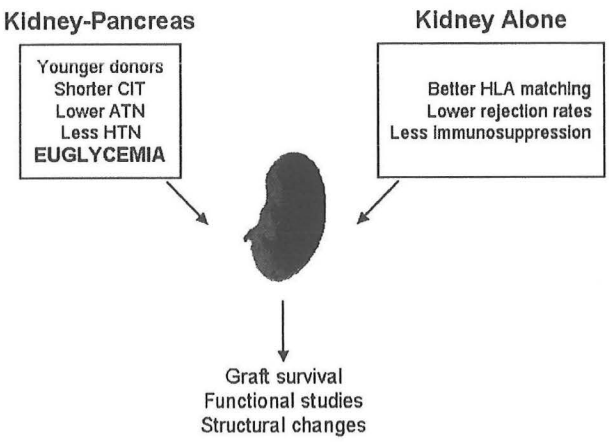

Figure 7: Renal Outcomes
(Partially adapted from Hrick, *Sem Nephrol* 20:188, 2000)

Renal allograft survival, functional renal assessment and histological evaluation are the three most important renal allograft outcomes. The most recent graft survival rates reported for recipients of SPK transplants of 91% are comparable to recipients of KTA [36]. Five-year renal graft survival rates are also similar for recipients of SPK and cadaveric renal transplants and higher than 70% in recent reports. Recipients of kidneys from HLA identical siblings have the lowest rates of acute rejection and delayed graft function and lowest creatinine at discharge and need for lower doses of immunosuppressive drugs and, therefore, show the best graft survival rates at 1 and 5 years post transplantation [97].

A recent report form UNOS data notes that SPK recipients with a functioning pancreas have a 45% reduction in renal graft failure (censored for death with a functioning graft) compared to SPK recipients who lose their pancreas during the first year after transplantation [104].

Single center studies of renal function after pancreas/kidney transplantation have revealed variable results. Some centers have reported no differences in renal function while others have noted a positive or negative impact in renal function for pancreas/kidney transplantation as compared to kidney transplantation alone [105,106,101,107,108]. Analysis of UNOS data suggests that the estimated creatinine clearance is higher and the average slope of deterioration in creatinine clearance less steep for pancreas/kidney recipients with a functioning pancreas than for pancreas/kidney recipients who lose their pancreas the first year after transplantation [104]. A recent report has noted that SPK recipients who lose their pancreas allograft during the first year after transplantation have a significant increase in urine albumin excretion at 10 years compared to SPK recipients with a functioning pancreas transplant [109].

Structural studies have provided valuable insights into the role of pancreas transplantation and glucose control in renal disease. In diabetic nephropathy there is accumulation of extracellular matrix in the mesangium, glomerular basement membrane (GBM), tubular basement membrane (TBM), and interstitium [109]. 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 (GFR) [109,110].

Mesangial and GBM lesions of diabetic nephropathy develop in kidneys from non-diabetic living and cadaver donors by 2 years after transplantation into diabetic recipients [111]. The relationship between hyperglycemia and diabetic lesions in renal transplant recipients is illustrated by the development of significantly higher increases in mesangial matrix (by 5 years after transplantation) in diabetic recipients treated with standard insulin therapy as compared to patients treated with an intensive insulin regimen (several insulin injections per day or continuous infusion via insulin pump) [112].

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 of recipients of PAK transplants [113,114].

PTA and Diabetic Nephropathy

Time	Baseline	5 years	10 years
UAE (mg/day)	103	30	20
CrCl (cc/min)	108	74	74
GBM thickness (nm)	594	570	404
Mesangial frac. vol.	0.33	0.39	0.27

Table 3: Data is from Fioretto et al., *NEJM* 339:69, 1998

The most interesting findings have been reported in a group of patients with type I diabetes and mild to advanced lesions of diabetic nephropathy but without uremia and who underwent pancreas transplantation alone (PTA) [115]. (See Table 3.) Kidney function studies and renal biopsies were performed at baseline, 5 and 10 years. Creatinine clearance decreased from baseline to 5 years but then remained stable. Urine albumin excretion decreased at 5 and 10 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 5 years. Nevertheless, 10 years after pancreas transplantation (and normoglycemia) the thickness of the GBM and TBM and the increased mesangial matrix decreased to normal and the nodular lesions of Kimmelstiel-Wilson disappeared [115].

The beneficial effects of pancreas transplantation in preventing diabetic nephropathy after transplantation may become more relevant as acute rejection rates decrease and renal allograft half-lives continue to improve.

Retinopathy

Many patients with diabetes and ESRD have advanced retinopathy and even blindness at the time of presentation for SPK transplantation [116,117]. 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. Nevertheless, a recent report has noted that more than 90% of patients with ESRD and diabetes who receive a SPK transplant have stabilization of diabetic retinopathy following transplantation [117]. SPK recipients with failed pancreas transplants appear to have higher rates of progression of retinopathy [117].

Diabetic microangiopathy in the conjunctival microcirculation improves by 18 months after transplantation in SPK transplant recipients, but not in diabetic recipients of kidney transplants alone [118]. The prevalence of cataracts of all types increases after transplantation [116,117,119].

Neuropathy

Diabetic neuropathy is characterized by progressive axonal loss manifested by diffuse somatic and autonomic abnormalities [120]. Successful pancreatic transplantation halts the progression of diabetic polyneuropathy in recipients of SPK, PAK and kidney transplants alone (KTA) [120,121]. A long-term study (10 years follow-up) from The University of Minnesota has shown that restoration of euglycemia 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 [120]. 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 [122]. Improvements in cardiac autonomic measures such as heart rate variability are particularly significant within the first year after SPK transplantation [123].

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 [124]. Nevertheless, changes toward normalization are mild probably due to previous structural damage to the peripheral nerves [120]. 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 [125].

Macrovascular Disease

Diabetic renal transplant candidates have a high incidence of atherosclerotic vascular disease and close to 1/3 of patients suffer a major vascular event, (myocardial infarction, cerebrovascular accident or amputation) by 3 years after the initial pre-transplant evaluation [126]. Vascular wall abnormalities increase over the years despite successful pancreas and kidney transplantation [127].

Studies comparing recipients of SPK transplants and kidney transplants alone have not shown benefits of pancreas transplantation in halting the progression of macrovascular diseases including coronary artery disease, cerebrovascular events or peripheral vascular complications [128,129].

Quality of Life

The main objective 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/kidney transplantation [130,131,132,133]. Patients with successful pancreas/kidney transplants also report higher quality of life than those pancreas/kidney recipients who have loss of the pancreas after transplantation [133].

A recent prospective observational study has provided valuable information on the impact of SPK transplantation as compared to kidney transplantation alone on quality of life issues [19]. After 3 years

of follow-up, most measures of health status and quality of life improved for both transplant groups. SPK patients reported greater improvements than kidney transplant alone patients in physical health and in diabetes-specific areas including satisfaction with health and therapy. Recipients of kidney transplant alone however, reported fewer emotional problems with role activities by 3 years post transplantation. The study could not determine if higher expectations from SPK patients (which were significantly more likely to be working by 1 year post transplantation) could have influenced the emotional scores [19].

Health-related quality of life measures for diabetic recipients of SPK transplants or kidney transplants alone do remain below that of the age-matched population [19,132].

Cost Effectiveness

Several advances in the last few years have led to reductions in costs for pancreas transplantation [134]. Improvements in surgical techniques and immunosuppression have made it possible to reduce post transplant complications, overall resource utilization and costs [134]. The expected 5-year costs are higher for SPK transplantation than for kidney transplantation alone [135]. Nevertheless, when incorporating all costs (such as managing diabetes) and patient preferences/quality of life adjustments, the most cost effective treatment for a patient with type I diabetes and ESRD is SPK transplantation [135]. Similarly, for diabetic patients with ESRD and who are interested in pancreas transplantation, SPK transplantation has been reported to be more cost effective than living-donor kidney transplantation followed by pancreas after kidney transplantation [136].

ISLET TRANSPLANTATION

Transplantation of islet cells is a much safer procedure than pancreas transplantation [137]. Autologous islet transplantation has been successful in preventing diabetes after pancreatic resection in patients with severe chronic pancreatitis or pancreatic tumors [138,139,140].

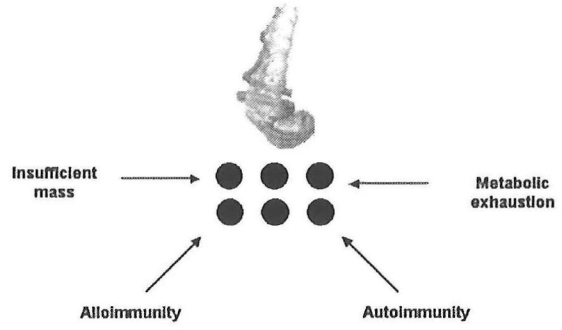

Figure 8: Islet Transplantation
(Adapted from Hering et al., *Graft* 1999)

The results of allogeneic transplantation of islet cells have been poor with less than 10% of recipients remaining insulin-free at one year post transplantation [141]. Important obstacles to allogeneic islet cell transplantation include low engrafted islet mass, immune-mediated destruction of islet tissue and metabolic exhaustion of islets [29,141].

Transplantation of islet cells is done after (collagenase) digestion of minced pancreas. A normal pancreas contains about 1 million islets but the number of viable islets is much lower after completion of the isolation procedures [141]. Isolated islets can then be injected into the portal vein or placed under the kidney capsule (in simultaneous recipients of kidney transplants) or intraperitoneally [23,138,139]. Relatively high numbers of cells have been used in most successful allogeneic islet transplants, but insulin secretory patterns are consistent with a reduced beta cell mass [142,143].

Immunity has been difficult to overcome in islet transplantation. Rejection is very common and difficult to detect, as hyperglycemia develops when more than 80-90% of the transplanted islet cell mass has become dysfunctional [141]. Even patients who undergo combined kidney-islet cell transplantation show this increase in immune reactivity with 100% acute kidney rejection rates reported in one series [144]. Autoimmunity also remains a problem in islet cell transplantation, and the presence of alloantibodies (such as anti-islet cell antibodies) correlates with islet graft failure [141,145].

Many immunosuppressive drugs including steroids, cyclosporine and tacrolimus are diabetogenic and promote insulin resistance [84,141]. In an insulin-resistant state a marginal mass of islet cells removed from their natural environment by the separation procedures cannot meet the metabolic demands and islet failure occurs [29,141].

A recent report from the University of Alberta has raised major hopes about pancreatic islet transplantation [146]. Seven patients with history of severe hypoglycemia and metabolic instability underwent islet transplantation under a steroid-free immunosuppressive regimen consistent of sirolimus, tacrolimus and an anti-interleukin-II receptor monoclonal antibody. Two cadaver donor pancreases were used to isolate islets for each recipient (3 cadaver donor pancreases required for one of the recipients). After a median follow-up of one year all recipients were insulin free with normal hemoglobin A1c levels and C-peptide concentrations. There were no hypoglycemic episodes or any serious complications from immunosuppression [146]. (See Table 4.) If these results can be consistently reproduced islet transplantation can become a clinical reality for diabetic patients in the future.

Islet Transplantation (Steroid Free)

Time	Baseline	3 months	6 months
HbA1c (%)	8.4	5.7	5.7
C-peptide (mg/ml)	<0.48	5.7	5.7

Table 4: Data from Shapiro et al., *NEJM* 343:230, 2000

There are millions of individuals affected by diabetes and a limited supply of islet cells from cadaver donors available. Progress in areas such as cultured human islet-cell lines, islet beta cell-expansion, transgenic/engineered beta cells and transplantation of xenogenic islets will be necessary to satisfy the demand for islet transplantation in the future [147,141].

CONCLUSION

Diabetes is the leading cause of ESRD in the U.S. Diabetic patients with ESRD experience high morbidity and mortality. Renal transplantation is superior to dialysis as therapy for ESRD and should be performed as early as possible in the course of ESRD.

Pancreas transplantation has become an established therapy which reliably restores euglycemia and insulin-independence to diabetic transplant recipients. Complications from pancreas transplantation although serious are becoming less common as surgical techniques, immunosuppressive drugs and medical care of transplant recipients continue to improve. Patients who receive a pancreas and

kidney transplant have a survival advantage over diabetic recipients of kidney transplants alone. Pancreas transplantation has beneficial effects in preventing diabetic nephropathy and in the course of diabetic neuropathy and diabetic retinopathy. Islet transplantation offers the promise of great benefits with lower risks for diabetic patients.

Diabetes and renal failure are two life threatening chronic medical conditions. Pancreas and kidney transplantation are therapies that can accomplish two very important medical objectives: restoration of sustained euglycemia and restoration of renal function. From a patient's perspective of quality of life, pancreas and kidney transplantation can also achieve some other very important objectives. Elimination of hypoglycemia, discontinuation of constant monitoring of plasma glucose, liberalization of dietary and fluid restrictions, independence from insulin therapy, and freedom from dialysis are important aspects in improving the care and quality of life of diabetic patients with ESRD.

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