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COPING WITH THE COMING PANDEMIC OF RENAL FAILURE DUE TO DIABETES MELLITUS

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Summary. *Europe is locked in the grip of a pandemic of diabetes that now engulfs the new world. In the United States (US), as well as Japan, and most nations in industrialized Europe, diabetes mellitus leads the causes of end-stage renal disease (ESRD). According to the latest US Renal Data System (USRDS) Report (2002), of 96,192 patients begun on therapy for ESRD during 2000, 41,772 (43.4%) had diabetes, an incidence rate of 145 per million population. Overall, survival of diabetic patients with ESRD has been improving annually over the past decade whether treated by peritoneal dialysis, hemodialysis, or a kidney transplant. Illustrating this point is the five year allograft function of 60.1% in diabetic cadaver kidney transplant recipients versus a five year allograft function of 60.3% of all recipients reported to the USRDS (1). This encouraging progress in therapy reflects multiple small advances in understanding of the pathogenesis of extrarenal micro- and macrovasculopathy in a previously inexorable disease, coupled with intensified regulation of hypertension and hyperglycemia. Identifying the perturbed biochemical reactions underlying the pathogenesis of diabetic vasculopathy – especially the adverse impact of accumulated advanced glycosylated end-products (AGEs) − raises the possibility of preempting end-organ damage without necessarily correcting hyperglycemia.*

Key words: *Diabetes mellitus, diabetic nephropathy, treatment*

Europe is locked in the grip of a pandemic of diabetes that now engulfs the new world. In the United States (US), as well as Japan, and most nations in industrialized Europe, diabetes mellitus leads the causes of end-stage renal disease (ESRD). According to the latest US Renal Data System (USRDS) Report (2002), of 96,192 patients begun on therapy for ESRD during 2000, 41,772 (43.4%) had diabetes, an *incidence* rate of 145 per million population (1) (Fig. 1). Reflecting their relatively higher death rate compared to other causes of ESRD, the *prevalence* of US diabetic ESRD patients on December 31, 2000, was 34% (131,173 of 378,862 patients). Both glomerulonephritis and hypertensive renal disease rank below diabetes in frequency of diagnosis among new ESRD patients, substantiating the contention of Mauer and Chavers that "Diabetes is the most important cause of ESRD in the Western world (2)".

The US Centers for Disease Control and Prevention (3), in its 2002 National Diabetes Fact Sheet states that more than 16 million people in the US have diabetes – one third of whom are unaware of their disorder. Among US adults, the prevalence of diagnosed diabetes increased 49% from 1990 to 2000. During 2003 in the US, an estimated 798,000 people will have newly diagnosed diabetes while 187,000 people will die from diabetes. Depending on age, race, and gender, diabetes in 1996 ranked from 8th (White men 45 to 65 years) to 4th (Black women 45 years and over) leading cause of death (4). Health care expenditures for diabetes in the US amount to a minimum of $100 billion and may be as high as $150 billion annually. The full impact of diabetic complications is unmeasured but in addition to the toll of ESRD includes 82,000 lower limb amputations, and 24,000 cases of blindness. It is highly probable that the Balkan nations will face a similar growth pattern in the incidence and prevalence of diabetes and diabetic complications.

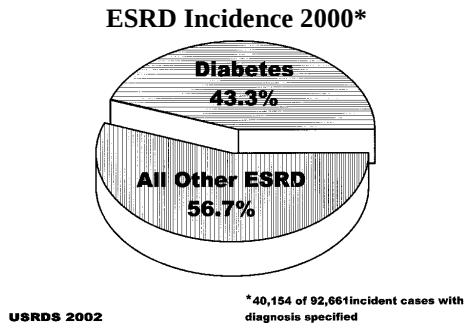

Fig. 1.

OPTIONS FOR ESRD TREATMENT IN DIABETES

Diabetic ESRD patients are managed similarly to nondiabetic ESRD patients with two exceptions: 1) simultaneous pancreas and kidney transplantation is a diabetes-specific therapy and 2) opting for no treatment, meaning electing passive suicide, is the choice more

often selected for and by diabetic than by nondiabetic individuals (Table 1). While the goal of uremia therapy is to permit an informed patient to select from a menu of available regimens, realities of program resources usually channel the diabetic ESRD patient to that treatment preferred by the supervising nephrologist. Illustrating this point, the first advocated option for newly treated ESRD is likely to be peritoneal dialysis performed as continuous ambulatory peritoneal dialysis (CAPD) in Toronto, home hemodialysis in Seattle, and a renal transplant in Minneapolis. In Mexico, where hemodialysis is severely limited, nearly all (of the relatively few) treated diabetic ESRD patients are assigned to peritoneal dialysis. No prospective, controlled trials of dialytic therapy – of any type – versus kidney transplantation have been reported or are likely to be initiated. Therefore, what follows reflects an acknowledged bias in interpreting the bias of others.

Confusion over diabetes type is frequent when evaluating diabetic ESRD patients. Underscoring the difficulty in determining diabetes type is the report that in Sweden, as many as 14% of cases originally diagnosed as noninsulin-dependent diabetes mellitus (type 2 diabetes) progressed to type 1 diabetes, while 10% of newly diagnosed diabetic individuals could not be classified (5). Islet ß-cell dysfunction in type 2 diabetes, noted in 27.2% of 56,059 subjects, varies with the different genetic defects associated with characteristic patterns of altered insulin secretion that can be defined clinically (6). Subjects with mild glucose intolerance and normal fasting glucose concentrations and normal glycosylated hemoglobin levels consistently manifest defective ß-cell function, a component of type 2 diabetes that is present before onset of overt hyperglycemia. The degree of hyperglycemia assessed by the level of hemoglobin A_{1c} (HbA_{1c}) is the best predictor of microvascular and macrovascular complications of diabetes (7). At the other extreme, it is well established that some patients with type 1 diabetes maintain a measurable level of pancreatic ß-cell activity for many years after onset of their disease (8) sometimes thwarting the utility of C-peptide measurements to distinguish type 1 diabetes from type 2 diabetes (9).

Diabetes in America and Europe is overwhelmingly type 2, fewer than seven percent of diabetic Americans are insulinopenic, C-peptide negative persons who have type 1 diabetes. ESRD in diabetic persons reflects the demographics of diabetes *per se* (10) in that: 1. The incidence (11) is higher in women, blacks (12), Hispanics (13), and native Americans (14). 2. The peak incidence of ESRD in diabetes occurs from the 5th to the 7th decade. Inferred from these relative attack rates, is the reality that blacks over the age of 65 face a seven times greater risk of diabetes-related renal failure than do whites. In the urban US, it is not surprising, therefore, that ESRD associated with diabetes is mainly a disease of poor, elderly blacks (15). Vasculopathic complications of diabetes including the onset and severity of hypertension are at least as severe in type 2 diabetes as in type 1 diabetes (16). In fact, recognition of the high prevalence of proteinuria and azotemia in carefully followed individuals with type 2 diabetes contradicts the view that type 2 diabetes only infrequently induces nephropathy (17). Although there are differences between type 1 diabetes and type 2 diabetes in terms of genetic predisposition (18) and racial expression, clinical expression of the two disorders - particularly manifestations of nephropathy - are remarkably similar as a correlate of disease duration.

Table 1. Options in uremia therapy for diabetic ESRD patients

1.	No Specific Uremia Intervention = Passive Suicide
2.	Peritoneal Dialysis
	Intermittent Peritoneal Dialysis (IPD)
	Continuous Ambulatory Peritoneal Dialysis (CAPD)
	Continuous Cyclic Peritoneal Dialysis (CCPD)
3.	Hemodialysis
	Facility Hemodialysis
	Home Hemodialysis
4.	Renal Transplantation
	Cadaver Donor Kidney
	Living Donor Kidney
5.	Pancreas plus Kidney Transplantation
	Type 1
?	Type 2

Careful observation of the course of nephropathy in type 1 and type 2 diabetes indicates strong similarities in rate of renal functional deterioration (19) and onset of comorbid complications. Early nephromegaly, as well as both glomerular hyperfiltration and microalbuminuria, previously thought limited to type 1 diabetes, are now recognized as equally prevalent in type 2 diabetes (20). Lack of precision in diabetes classification provokes confusing terms like "insulin requiring" to explain treatment with insulin in persons thought to have *resistant* type 2 diabetes. In fact, present criteria are unable to classify as many as one-half of diabetic persons as specifically type 1 or type 2 diabetes (21,22). Consequently, literature reports of the outcome of ESRD therapy by diabetes type are few and imprecise.

CO-MORBID RISK FACTORS

Management of a diabetic person with progressive renal insufficiency is more difficult than in an age and gender matched nondiabetic person. The toll of coincident extrarenal disease – especially blindness, limb amputations, and cardiac disease – limits or preempts rehabilitation. For example, provision of a hemodialysis vascular access in a nondiabetic patient is minor surgery, whereas a diabetic patient, after even minimal surgery, risks major morbidity from infection or deranged glucose regulation. As a group, diabetic patients manifesting ESRD suffer a higher death rate due to cardiac decompensation, stroke, sepsis and pulmonary disease than do nondiabetic ESRD patients.

Listed in Table 2 are the major co-morbid concerns in the management of diabetic ESRD patients. Diabetic

retinopathy ranks at the top – with heart and lower limb disease – as major concerns in overall patient care. More than 95 per cent of diabetic individuals, in industrialized countries where advanced healthcare is readily available, who begin maintenance dialysis, or receive a renal allograft, have undergone laser treatment and/or vitrectomy surgery for retinopathy. Laser and/or vitreous surgery are best integrated as a component of comprehensive management (Fig. 2) (23). Consultation – even in asymptomatic patients – with a collaborating cardiologist familiar with uremia in diabetic patients defines the timing of usually required heart evaluation. Coronary angiography (if indicated), will detect those for whom prophylactic coronary artery angioplasty or bypass surgery is likely to extend life. Similarly, the renal team should include a podiatrist who delivers regular surveillance of patients at risk of major lower extremity disease, thereby reducing the risk of amputations, a complication noted in about 20% who do not receive podiatric care. Autonomic neuropathy – expressed as gastropathy, cystopathy, and orthostatic hypotension – is a frequently overlooked, highly prevalent disorder impeding life quality in the diabetic with ESRD. Diabetic cystopathy, though common, is frequently unrecognized and confused with worsening diabetic nephropathy and is sometimes interpreted as allograft rejection in diabetic kidney transplant recipients. In 22 diabetic patients who developed renal failure – 14 men and 8 women of mean age 38 years – an air cystogram detected cystopathy in 8 (36%) manifested as detrusor paralysis in 1 patient; severe malfunction in 5 patients (24%)); and mild impairment in 1 patient. Older male patients should be examined to exclude a prostatic component of obstruction. Encouragement to the patient adapting to a regimen of frequent voiding and self-application of manual external pressure above the pubiic symphysis (Crede Maneuver) plus administration of oral bethanechol usually permits resumption of spontaneous voiding. Finally, repeated self-catheterization of the bladder may be the only means to avoid an indwelling catheter when an atonic bladder is unresponsive to the above protocol.

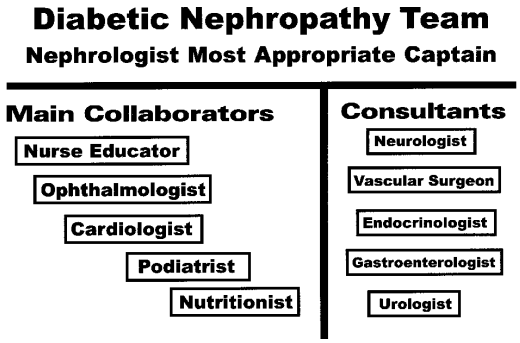

Fig. 2.

Gastroparesis afflicts one-quarter to one-half of azotemic diabetic persons when initially evaluated for renal disease (24). Other expressions of autonomic neuropathy – obstipation and explosive nighttime diarrhea – often coexists with gastroparesis (25). Obstipation responds to daily doses of cascara, while diarrhea is treated with psyllium seed dietary supplements one to three times daily plus loperamide (26) in repetitive 2 mg. doses until symptoms abate or a total dose of 18 mg daily.

Table 2. Diabetic complications which persist and/or progress during ESRD

1.	Retinopathy, glaucoma, cataracts
2.	Coronary artery disease. Cardiomyopathy
3.	Cerebrovascular disease
4.	Peripheral vascular disease: limb amputation
5.	Motor neuropathy. Sensory neuropathy
6.	Autonomic dysfunction: diarrhea, dysfunction, hypotension
7.	Myopathy
8.	Depression

Cardiovascular Disease

Heart disease, the leading cause of death among patients with diabetes mellitus, is often advanced at the time of a candidate's initial consideration for transplantation and can certainly progress during the years a patient awaits organ availability on the cadaver waiting list. Khauli et. al. identified 38% of diabetic ESRD patients with coronary artery disease, in 1986, an era of far more conservative referral and exclusions of obese and/or aged transplant candidates than the current approach (27). Failure to recognize critical heart disease may lead to loss of the allograft and the patient's demise. Presence of minimal pump dysfunction or angiographically demonstrable coronary artery lesions that are either asymptomatic or responsive to drugs, need not preclude transplantation so long as expectations are realistic and management fastidious. In fact, successful engraftment of a renal transplant may induce overall improvement in the diabetic recipient's cardiac function. Indeed, Abbott et. al. reported a lower risk of hospitalization for congestive heart failure after transplantation when compared to patients with ESRD due to diabetes on the renal transplant waiting list (28).

Determination of the specific individual's overall level of cardiac risk in advance of transplantation, a surgical procedure that may be associated with hemodynamic instability, hemorrhage, prolonged anesthesia, reoperation to address technical complications, hypertension and infection, is crucial as the patient and transplant team assess whether or not an organ transplant is a reasonable option. Should severe coronary artery disease be discovered, revascularization of the myocardium by coronary artery bypass or angioplasty becomes an absolute requirement in preparation for transplantation (29). Khauli et. al. first reported the use of coronary angiography for detecting the presence and severity of coronary artery disease and left ventricular dysfunction in 48 diabetic patients scheduled for a kidney transplant. The benefit of pre-transplant myocardial revascularization was inferred from the uni-

form successful outcome in 23 diabetic patients, none of whom died. The remarkably good two-year patient and graft survival for living donor and cadaver donor recipients given "standard" immunosuppression with azathioprine and prednisone was 81% and 68%, and 61% and 32%, respectively.

We concur with Philipson et. al. who studied 60 diabetic patients being considered for a kidney transplant and advised that "patients with diabetes and end-stage renal disease who are at highest risk for cardiovascular events can be identified, and these patients probably should not undergo renal transplantation (30)." The basis for this position was an analysis of treatment outcome in which only seven patients had a negative thallium stress test, four of whom received a kidney transplant, without subsequent "cardiovascular events'. By contrast, of 53 diabetic patients with either a positive or nondiagnostic stress thallium tests, cardiac catheterization was employed to identify 26 patients with mild or no coronary disease or left ventricular dysfunction; 16 patients in this group received kidney transplants without cardiovascular incident. In a subset of ten patients with moderate heart disease, of whom 8 received renal transplants, two died of heart disease, while of thirteen patients with severe coronary artery disease or left ventricular malfunction, eight died before receiving a transplant, three from cardiovascular disease.

SELECTING UREMIA THERAPY

Depending on age, severity of co-morbid disorders, available local resources, and patient preference, the uremic diabetic patient may be managed according to different protocols (Fig. 3). Diabetic ESRD patients select the no further treatment option, equivalent to passive suicide, more frequently than do nondiabetic patients (31). Such a decision is understandable for blind, hemiparetic, bed-restricted limb amputees for whom life quality has been reduced to what is interpreted as unsatisfactory. On the other hand, attention to the total patient may restore a high quality of life that was unforeseen at the time of ESRD evaluation (32).

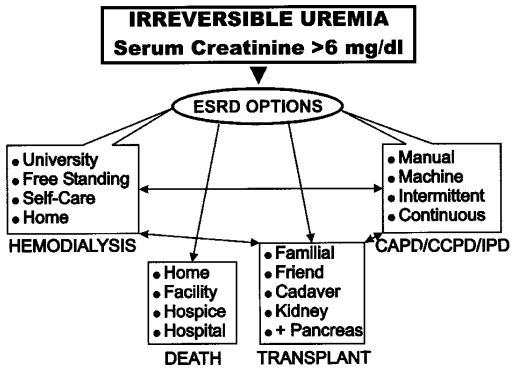

Fig. 3.

Hemodialysis

Unfortunately, in both Europe and the US, so called "preterminal care in diabetic patients with ESRD" is deficient in amount and quality (33) with inadequate attention to control of hypertension, hyperlipidemia or ophthalmologic intervention (34). For the large majority – over 80% of diabetic persons who develop ESRD in the US – maintenance hemodialysis is the only renal replacement regimen that will be employed. Approximately 12% of diabetic persons with ESRD will be treated by peritoneal dialysis while the remaining 8% will receive a kidney transplant. To perform maintenance hemodialysis requires establishment of a vascular access to the circulation. Creation of what has become the *standard access* – an internal arteriovenous fistula in the wrist – is often more difficult in a diabetic than in a nondiabetic person because of advanced systemic atherosclerosis. For many diabetic patients with peripheral vascular calcification and/or atherosclerosis, creation of an access for hemodialysis necessitates resort to synthetic (Dacron) prosthetic vascular grafts.

The typical hemodialysis regimen requires three weekly treatments lasting 4 to 5 hours each, during which extracorporeal blood flow must be maintained at 300 to 500 ml/min. Motivated patients trained to perform self-hemodialysis at home gain the longest survival and best rehabilitation afforded by any dialytic therapy for diabetic ESRD. When given hemodialysis at a facility, however, diabetic patients fare less well, receiving significantly less dialysis than nondiabetic patients due, in part, to hypotension and reduced access blood flow (35). Maintenance hemodialysis does not restore vigor to diabetic patients as documented by Lowder et al., in 1986, who reported that of 232 diabetics on maintenance hemodialysis, only seven were employed, while 64.9 per cent were unable to conduct routine daily activities without assistance (36). Approximately 50% of diabetic patients begun on maintenance hemodialysis die within two years of their first dialysis.

Peritoneal Dialysis

In the US, peritoneal dialysis sustains the life of about 12% of diabetic ESRD patients. Continuous ambulatory peritoneal dialysis (CAPD) holds the advantages of freedom from a machine, performance at home, rapid training, minimal cardiovascular stress and avoidance of heparin (37). To permit CAPD, an intraperitoneal catheter is implanted one or more days before CAPD is begun. Typically, CAPD requires exchange of 2 to 3 liters of sterile dialysate, containing insulin, antibiotics, and other drugs, 3 to 5 times daily. Mechanical cycling of dialysate, termed continuous cyclic peritoneal dialysis (CCPD) can be performed during sleep.

CAPD and CCPD pose the constant risk of peritonitis as well as a gradual decrease in peritoneal surface area. Some clinicians characterize CAPD as "a first choice treatment" for diabetic ESRD patients (38). A less enthu-

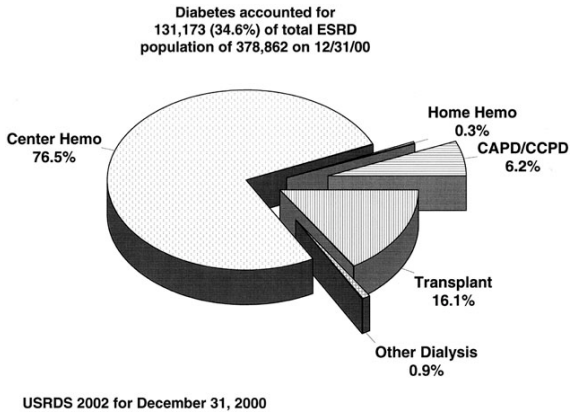

Fig. 4.

siastic judgment of the worth of CAPD in diabetic patients was made by Rubin et al. in a largely black diabetic population treated with CAPD in Jackson, Mississippi (39). Only 34% of patients remained on CAPD after two years, and at three years, only 18% continued on CAPD. According to the USRDS, survival of diabetic ESRD patients treated by CAPD is significantly less than on hemodialysis. A decision to select CAPD, therefore, must be individual-specific after weighing its benefits including freedom from a machine and electrical outlets, and ease of travel against the disadvantages of unremitting attention to fluid exchange, constant risk of peritonitis, and disappearing exchange surface. As concluded in a Lancet editorial: "Until the frequency of peritonitis is greatly reduced, most patients can expect to spend only a few years on CAPD before requiring a different form of treatment, usually haemodialysis (40)."

Evaluation of Transplant Candidacy

Armed with the knowledge that transplantation of a kidney and, perhaps, a pancreas, is the sole renal replacement therapy offering the uremic diabetic substantial likelihood of prolonged survival, the transplant team bears the onus of excluding only those candidates for whom the moderate technical demands of the transplant operation are anticipated to be excessively risky, or those individuals with comorbidities that are anticipated to be worsened substantially by the requisite use of pharmacologic immunosuppression. The consensus that offering access to the scarce pool of cadaveric organs to patients who are far older and sicker than the ideal, young candidates transplanted in earlier eras is now justifiable, has developed sequentially. With steadily improving outcomes, refinement of anti-rejection drug therapies, and the pioneering efforts of individual transplant groups who advocated on behalf of specific population segments (after the model of the Minnesota transplant team that first demonstrated that diabetes was not an insurmountable risk factor) (41), renal transplantation must now be weighed as an option in the management of every Medicare covered ESRD patient. Accordingly, the transplant candidate is not approached with the expectation that indefinite longevity, full sight or independent ambulation must be anticipated in order to vindicate allocation of an organ to that individual. We continue to consider the presence of ongoing systemic infection that is likely to compromise short or immediate term survival of the patient or organ, the presence of malignancy that is likely to be progressive in the presence of immunosuppression, or the inability to comprehend or comply with the post-transplantation regimen of medication utilization or medical supervision needed to protect the engrafted organ or its host, as the principle contraindications to acceptance of a transplant candidate (Table 3).

Table 3. Evaluation of transplant candidacy for diabetic esrd patients

Absolute Contraindications
Acute systemic infection (bacterial, fungal or viral)
Progressive malignancy
Likely survival < 2 years
Inability to comply with medications or medical advice
Inability to give informed consent
Relative Contraindications
Age > 70 years
Body Mass Index > 40
Unreconstructable Coronary Artery Disease
Incurable chronic infection (HIV, hepatitis C, hepatitis B)
Indolent malignancy (e.g., prostate cancer, multiple non-melanoma skin cancers)

Pancreas Transplantation

The largest data repository from which data regarding the outcome of pancreas transplantation may be gleaned is the International Pancreas Transplant Registry (IPTR), now reporting on >17,000 transplants of which 11,500 were performed in the U.S. (42). Solitary pancreas transplantation (PTA; pancreas transplant alone) represents only 5% of reported cases with the lowest one year graft survival (78%). Transplanting a cadaver donor pancreas in a recipient with a functioning renal allograft (PAK; pancreas after kidney) is the most popular strategy for candidates with a living kidney donor even though two separate operations are required and represented 13.2% of cases. Superior pancreatic graft survival is reported for SPK (simultaneous cadaveric pancreas and kidney) over PAK recipients; 83 vs. 79%, inter group differences such as 1) duration of pre-transplant maintenance dialysis 2) duration of state of immunosuppression prior to pancreas transplantation and 3) HLA identity or difference of renal and pancreatic donors probably contribute to this perhaps insignificant difference. Pancreatic duct management in the US is predominantly by enteric drainage (as opposed to bladder drainage) in SPK transplants (67%) vs 51% for PAK and 42% for PTA, the type of duct drainage did not affect graft survival rates. Pancreatic allograft loss from rejection is declining in frequency, currently 4%, 6% and 8% per year for SPK, PAK and PTA, respectively. Unfortunately, pancreas transplantation per-

formed in patients with extensive extrarenal disease, has neither arrested nor reversed diabetic retinopathy, diabetic cardiomyopathy, or extensive peripheral vascular disease (43).

Reports of beneficial effects on visual acuity and the need for additional posttransplant laser therapy are generated principally from patients with more mild disease (44). The most remarkable result is that patient survival from all pancreas transplants in the US in the most recent era (1997 – 2001) is > 95% (41).

Combined Pancreas Plus Kidney Transplantation

For many uremic individuals with type 1 diabetes, a combined kidney plus pancreas transplant has evolved as an important option because of its ability to offer superior glycemic control and improved quality of life. As both kidney graft survival and overall mortality are approximately equivalent following kidney alone versus dual organ transplantation alone at many centers, neither the survival of the patient nor the success of the kidney transplant need be jeopardized by the addition of a pancreas graft. It is true that recipients of combined pancreas plus kidney grafts experience greater morbidity, a reality that can be justified by the evidence that a pancreas graft will both prevent recurrent diabetic nephropathy, and may result in improvements in sensory/motor neuropathy.

Following simultaneous pancreas kidney transplants, but not after a kidney transplant alone, hyperlipidemia reverts to normal, affording a hint of perhaps better cardiovascular outcomes as well. In those with normal or only mild renal disease, the decision to proffer an isolated pancreas transplant is more complex. Consistently, success rates for solitary pancreas transplants are lower than after combined simultaneous or dual sequential organ transplants. Suitable candidates for an isolated pancreas graft are those younger than 45 years suffering repeated bouts of disabling hypoglycemia or ketoacidosis unresponsive to other measures. More difficult to judge is whether or when individuals who have advancing diabetic complications with relatively intact renal function (creatinine clearance >60mL/min) should be considered for an isolated pancreas transplant. An encouraging report from the Minnesota Transplant Team observed that a successful pancreas transplant after five or more years of euglycemia will reverse established pathologic changes of diabetic nephropathy including disappearance of nodular glomerular lesions (45). At ten years, eight patients with type I diabetes and normal glycosylated hemoglobin values achieved with pancreas transplantation, progressive reduction in the median urinary albumin excretion rate, in the thickness of the glomerular and tubular basement membranes, and in the mesangial fractional volume – a remarkable accomplishment (46). Pancreas transplantation is an important option in the treatment of type 1 diabetes so long as alternative strategies to provide equal glycemic control with less or no immunosuppression or less overall morbidity remain elusive.

Transplantation of Pancreatic Islets

The main attraction of pancreatic islet over whole organ pancreas transplantation as a diabetes cure is the potential technical simplicity and avoidance of the risks of a major surgical procedure by simple injection of a small volume suspension of islets. Pancreatic islets are durable. Insulin-producing islets can be isolated with a relatively simple and reproducible technique utilizing enzymatic digestion (trypsin) of the whole pancreas in rodent, canine and primate species. Human islets are also culled by mincing and enzyme digestion of normal pancreas glands obtained from cadaver donors (47), or resected for disease (48). Freshly isolated islets can be safely transported across great distances meaning that the isolation laboratory need not be located at, or even in proximity, to the transplant center.

Heterotopic sites employed in rodent, dog and primate trials of islet implantation included: the peritoneum (49), thymus (50), testicle (51,52) spleen (53) kidney capsule (54), and liver (55) but only the last two are clinically practical; the liver is preferred. Underscoring the longevity of pancreatic islets is the use of intrahepatic autotransplanted islets from pancreas glands removed to treat chronic pancreatitis successfully preventing endocrine insufficiency (56). Technically successful islet transplants may undergo progressive graft loss presumed associated with their ectopic location such as nutritional toxins, intestinal bacteria and endotoxins. Most exciting has been the impressive recent experience with clinical human islet transplantation reported by the Edmonton, Alberta group (57). Using a steroid immunosuppressive protocol including baslixiximab, sirolimus and tacrolimus, insulin independence beyond 1 year has been achieved with transplantation of a minimum of 9,000 islets/kg (this often requires sequential transplantation from islets procured from more than 1 pancreas) in 12 type 1 diabetics. This first clinical success has provoked renewed enthusiasm for an approach that is well tolerated and is distinctly less morbid than whole organ transplantation.

Pancreas Transplantation for Type 2 Diabetes

Until the past 7 to 8 years, pancreas transplantation in type 2 diabetic recipients was thought contraindicated because of their persistent secretion of insulin. The pathophysiologic problem in type 2 disease was attributed to insulin resistance rather than insulin lack. Furthermore, advanced age and obesity, usually present in type 2 diabetes, are associated with increased morbidity and mortality from all surgical procedures and specifically following pancreas transplantation (58). Further apprehension over the wisdom of performing a pancreas transplant in type 2 recipients is the fear that exposure of donor beta cells to an environment of insulin resistance will promote their overstimulation and ultimate exhaustion meaning functional graft loss (59). Sasaki et al report a fascinating experience with 13 intentional simultaneous pancreas-kidney transplants in recipients with elevated C-peptide levels

establishing their diabetes as type 260. Graft survival in these type 2 diabetic recipients was an impressive 100% with a mean follow-up of 46 months. The IPTR experience reports 5% of pancreas transplants were performed for type 2 diabetes with graft survival rates equal to those in type 1 patients (60).

PATIENT SURVIVAL DURING TREATMENT OF ESRD

Prospective studies of renal transplantation compared with peritoneal or hemodialysis do not overcome limitations imposed by patient and physician refusal to permit random assignment to one treatment over another. As a generalization, younger patients with fewer complications are assigned to renal transplantation while residual older, sicker patients are treated by dialysis. Combined kidney/pancreas transplants are restricted (with rare exploratory exceptions) to those with type 1 diabetes who are younger than age 50. Reports from the European Dialysis and Transplant Association (EDTA) Registry, summarized by Brunner et al., demonstrate the singular and understandable effect of age on survival during treatment for ESRD "irrespective of treatment modality and of primary renal disease (61)." At 10 and 15 years after starting treatment, 58% and 52% respectively of patients who were 10 to 14 years old when begun on ESRD therapy were alive, compared to 28% and 16% who were alive at 10 and 15 years of those who were 45 to 54 years old when starting ESRD therapy. A similar effect of increasing age is noted in recipients of living related donor kidney transplants. In the early 1980s, kidney recipient survival was 92% at 5 years for patients younger than 15, 87% for the 15 to 44 year old cohort and 72% for those aged 45 or older.

Overall patient and graft survival following renal transplantation continue to slowly rise thanks to advances in overall medical care and, more specifically, to improved therapeutic windows associated with modern immunosuppressive agents such as sirolimus, mycophenolic acid and basiliximab. Graft survival for diabetic recipients of living donor kidneys is currently 95% and 89% at 1 and 3 years, versus 90% and 79% at 1 and 3 years after cadaver donor kidneys (62). Early outcomes do not differ between diabetics and non-diabetics; collective graft survival rates of transplants performed between 1996 – 2001 in the U.S. are 90.2% for diabetics at 1 year, versus rates of 88.5 – 93.4% for patients with all other diagnoses. Long-term, however, diabetics have a lower survival rate, due principally to deaths from cardiovascular disease. Rajagopalan and colleagues observed equivalent graft survival between diabetics and non-diabetics ten years after kidney transplantation, though patient survival was 10% lower among diabetics (63). Although the long-term prognosis is limited for diabetics, it is clear from groups like Hypolite et.al. (64) 83 reporting a decreased likelihood of hospitalization for acute coronary syndromes for diabetics after renal transplantation (0.79% per patient year) compared to those still on the waiting list (1.67% per patient year), that those diabetics who acquire kidney transplants have optimized their chances of survival.

Diabetes adds a severe restriction on life anticipation, imparting a threefold rise in risk of dying compared with either chronic glomerulonephritis or polycystic kidney disease. In England, diabetic and nondiabetic patients starting CAPD or hemodialysis in seven large renal units between 1983-1985 were monitored prospectively over four years. Of 610 new patients (median age 52 years, range 3-80 years) beginning CAPD and 329 patients (median age 48 years, range 5-77 years) starting hemodialysis, patient survival estimates at 4 years were 74% for hemodialysis and 62% for CAPD (65). Survival on CAPD and maintenance hemodialysis is lower in the U.S. than in Europe. An explanation for diabetic dialysis patients' better survival in Europe is not evident, though the growing application of American practices of dialyzer reuse and shortened treatment hours have been incriminated as promoting fatal underdialysis (66).

The case for or against CAPD as a preferred therapy is still open. On the positive side, for example, is the report of Maiorca et al. who detailed an 8 year experience at a single center in Italy which offered "all treatments" for ESRD (67). Survival at 5 years was equivalent for CAPD and hemodialysis patients but 98% of those started on hemodialysis continued hemodialysis while only 71% of CAPD treated patients remained on CAPD ($p<0.01$). Contending that survival on hemodialysis or CAPD is now equivalent, Burton and Walls determined life-expectancy using the Cox Proportional Hazards statistical methodology for unequal group analysis in 389 patients accepted for renal replacement therapy in Leicester between 1974 and 1985 (68). There were no statistically significant differences between the relative risk of death for patients on CAPD (1.0), those on hemodialysis (1.30), and those who received a kidney transplant (1.09). CAPD, the authors concluded "is at least as effective as haemodialysis or transplantation in preserving life." For the present substantiation of the superiority of one ESRD treatment over another is lacking whether for the total population of ESRD patients or for the subset with diabetic nephropathy (Table 3) (69).

CO–MORBID INDEX FOR DIABETIC PATIENTS

To aid in grading the course of diabetic patients over the course of ESRD treatment we inventory the type and severity of common co-morbid problems. Numerical ranking of this inventory constitutes a co-morbid index (Table 4). As remarked above, comparison between treatments (hemodialysis versus CAPD (70) versus renal transplantation versus combined kidney and pancreas transplantation) demands that patient subsets be equivalent in severity of illness before application of the treatment modality under study.

Table 4. Morbidity in diabetic kidney transplant recipientsthe co-morbidity index

1) Persistent angina or myocardial infarction.
2) Other cardiovascular problems, hypertension, congestive heart failure, cardiomyopathy.
3) Respiratory disease.
4) Autonomic neuropathy (gastroparesis, obstipation, diarrhea, cystopathy, orthostatic hypotension).
5) Neurologic problems, cerebrovascular accident or stroke residual.
6) Musculoskeletal disorders, including all varieties of renal bone disease.
7) Infections including AIDS but excluding vascular accesssite or peritonitis.
8) Hepatitis, hepatic insufficiency, enzymatic pancreatic insufficiency.
9) Hematologic problems other than anemia.
10) Spinal abnormalities, lower back problems or arthritis.
11) Vision impairment (minor to severe - decreased acuity to blindness) loss.
12) Limb amputation (minor to severe - finger to lower extremity).
Mental or emotional illness (neurosis, depression, psychosis). To obtain a numerical Co-Morbidity Index for an individual patient, rate each variable from 0 to 3 (0 = absent, 1 = mild - of minor import to patient's life, 2 = moderate, 3 = severe). By proportional hazard analysis, relative significance of each variable isolated from the other 12.

Only limited data suggests an advantage other than well being for strict metabolic control once uremia has developed. On the other hand, it is reasonable to anticipate that all of the benefits to native kidneys of blood pressure and blood glucose control should be conferred on a renal transplant, retarding the recurrence of diabetic nephropathy in the kidney allograft. In a comparison of renal transplant biopsies taken ≥ 2.5 years post-transplant, 92% of recipients of a combined pancreas and renal transplant but only 35% of recipients with renal transplant alone had normal glomerular basement membrane thickness (71). Glomerular mesangial volume expansion in the renal transplant, another early sign of recurrent diabetic nephropathy, is also retarded by the presence of a functioning pancreatic transplant. Anemia in azotemic diabetic patients adds to comorbidity and is responsive to treatment with recombinant erythropoietin. Concern over a possible increase in severity of hypertension as red cell mass increases is based on an early finding that ambulatory maintenance hemodialysis patients evince such a change (72). To expedite management of the myriad micro- and macrovascular complications that are manifested as azotemia increases, an orderly approach is advised. Subsequent selection of ESRD therapy for a diabetic individual whose kidneys are failing requires appreciation of the patient's family, social, and economic circumstances. Home hemodialysis, for example, is unworkable for a blind diabetic who lives alone. Deciding upon a kidney transplant requires knowledge of the patient's family structure, including its willingness to participate by donating a kidney. Without premeditation, the diabetic ESRD patient is subjected to repetitive, inconclusive studies instead of implementation of urgently required treatment (such as panretinal photocoagulation or arterial bypass surgery).

Autonomic Neuropathy

Throughout transplant surgery, and the day or two before oral feeding is resumed, metabolic control of plasma glucose concentration is best effected by frequent hourly (when needed) measurements of glucose and an intravenous infusion of 1-4 units per hour of regular insulin. Bethanechol, which may be given in combination with metoclopramide also improves gastric motility. Constipation, sometimes evolving into obstipation, is a frequent problem following transplantation. Effective stimulants to resume spontaneous defecation are early ambulation, stool softening agents, and suspension of cascara. Autonomic neuropathy may, at the other extreme, induce explosive and continuous liquid diarrhea enervating and dehydrating the post-operative diabetic patient. With the high incidence of clostridium difficile infection among hospitalized patients often exacerbating symptoms we find that loperamide given hourly in doses as high as 4 mg/hr almost always halts diarrhea.

A Life Plan (73) may elect "no treatment" when life extension is unacceptable. Illustrating this point, a blind, hemiparetic diabetic patient experiencing daily angina and nocturnal diarrhea, who is scheduled for bilateral lower limb amputation may chose death despite his family's plea that he start maintenance dialysis. Because azotemic diabetic patients typically are depressed, however, a rational decision to die must be distinguished from temporary despair over a current setback. Despondent diabetics, on occasion, respond to visits by rehabilitated dialysis patients or transplant recipients by reversing their decision to die. It is unwise to coerce acceptance of dialysis or a kidney transplant, when life has minimal (or even negative) value. Diabetic patients forced into uremia therapy by family or the health care team are often noncompliant to dietary and drug regimens, thereby expressing behavior culminating in passive suicide.

Pregnancy

Pregnancy, rare among ESRD patients on dialysis, make occur following successful transplantion. The National Transplantation Pregnancy Registry (NPTR) includes 31 female pancreas-kidney recipients who bore 45 pregnancies with an 80% rate of live births; 53% of births occurred with Cesarean sections. While 75% of births were premature (less than 37 weeks of gestation), 57% of babies had low birthweight (< 2500 grams), and 53% of newborns had complications only 1/36 died. There is a substantial (8%) risk of a rejection episode during the pregnancy, and a 16% rate of graft loss within 2 years of delivery. Remarkably, all pancreatic allografts supported pregnancies without the development of hyperglycemia. Data for pregnancies among female kidney recipients are similar although specific outcomes for diabetic recipients are not available (74).

REHABILITATION

Inferences extracted from the study of rehabilitation in the diabetic ESRD patient are that: 1) Patients fare best when participating in their treatment regimen. 2) A functioning renal transplant permits markedly superior rehabilitation than that attained by either peritoneal dialysis or hemodialysis (Fig. 5). Unfortunately, bias in assignment to a specific treatment may have prejudiced the favorable view of kidney transplants to the extent that statistical corrections (Cox Proportional Hazards technique) cannot compensate for group differences.

Treating ESRD Due to Diabetes*

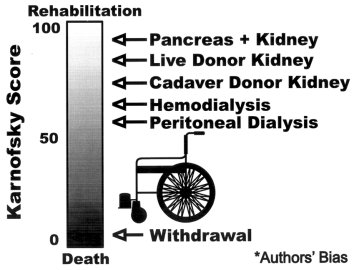

Fig. 5.

Studies in which the mean age of transplant patients is a decade younger than the CAPD or hemodialysis groups are likely to discern better functional status in the younger group. Another variable affecting the magnitude of rehabilitation attained in diabetic and nondiabetic ESRD patients is the progressive increase in age of newly treated patients. In the US, for example, patients over the age of 69 years who comprised 27% of all dialysis patients in 1979, increased by 450% between 1974 and 1981, and will make up 60% of all dialysis patients by the year 2010. An ageing ESRD population has a declining rate of employment and increasingly prevalent comorbid complications. An extremely optimistic picture of rehabilitation during maintenance hemodialysis was projected by a state-wide longitudinal prospective study of 979 ESRD patients in Minnesota in which the Karnofsky scoring system (75) was employed to assess patient well being (76). Initial Karnofsky scores showed that 50% of all patients were able to care for themselves when starting treatment. After two years of maintenance hemodialysis, a remarkable 78% of patients maintained or improved their functional status. Kidney transplant recipients, however, had higher initial Karnofsky scores than did those relegated to long-term dialysis. Selection for a kidney transplant gleaned the most functional patients leaving a residual population of less functional patients. Thereafter, comparisons of relative rehabilitation in transplant and dialysis groups are flawed by selection bias favoring kidney transplant recipients.

The Minnesota description of well being on maintenance hemodialysis is highly atypical. Sustaining this point, for example, is the nationwide survey of maintenance hemodialysis patients, in which Gutman, Stead and Robinson measured functional assessment in 2,481 dialysis patients irrespective of location or type of dialysis (77). Diabetic patients achieved very poor rehabilitation; only 23% of diabetic patients (versus 60% of nondiabetic patients) were capable of physical activity beyond caring for themselves. Lowder et al discerned the same very low level of rehabilitation (23). More recent confirmation of this point was afforded by Ifudu et al. who documented pervasive failed rehabilitation in a multicenter studies of diabetic and nondiabetic (78), and elderly inner-city (79) hemodialysis patients. The inescapable conclusion of studies to date is that maintenance hemodialysis, in most instances, does not permit return to life's responsibilities for diabetic individuals.

Advanced Glycosylated Endproducts

In health, protein alteration resulting from a nonenzymatic reaction between ambient glucose and primary amino groups on proteins to form glycated residues called Amadori products is termed the Maillard reaction. After a series of dehydration and fragmentation reactions, Amadori products are transformed to stable covalent adducts called advanced glycosylation endproducts (AGEs). In diabetes, accelerated synthesis and tissue deposition of AGEs is proposed as a contributing mechanism in the pathogenesis of clinical complications (80). Accumulation of AGEs in the human body is implicated in aging and in complications of renal failure (81) and diabetes (82). AGEs are bound to a cell surface receptor (RAGE) inducing expression of vascular cell adhesion molecule-1 (VCAM-1), an endothelial cell surface cell-cell recognition protein that can prime diabetic vasculature for enhanced interaction with circulating monocytes thereby initiating vascular injury (83).

Glomerular hyperfiltration, characteristic of the clinically silent early phase of diabetic nephropathy may be induced by Amadori protein products – in rats, infusion of glycated serum proteins induces glomerular hyperfiltration (84). Nitric oxide, produced by endothelial cells, the most powerful vasodilator influencing glomerular hemodynamics (85), has enhanced activity in early experimental diabetes (86). Subsequently, AGEs, by quenching nitric oxide synthase activity, limit vasodilation and reduce glomerular filtration rate (87). Clarification of the interaction of AGEs with nitric oxide may unravel the mystery of the biphasic course of diabetic glomerulopathy – sequential hyperfiltration followed by diminished glomerular filtration.

Pharmacologic prevention of AGE formation is an attractive means of preempting diabetic microvascular complications because it bypasses the necessity of having to attain euglycemia, an often unattainable goal. Pimagidine (aminoguanidine), interferes with non-enzymatic glycosylation (88) and reduces measured AGE levels leading to its investigation as a potential treatment. Pimagidine was selected because its structure is similar to α-hydrazinohistidine, a compound known to reduce diabetes-induced vascular leakage, while having opposite effects on histamine levels (89).

Pimagidine treatment in rats made diabetic with streptozotocin preempts complications viewed as surrogates for human diabetic complications. Representative examples from a large literature include: 1) Preventing development of cataracts in rats 90 days after being made "moderately diabetic" (<350 mg/dl plasma glucose); lens soluble and insoluble AGE fractions were inhibited by 56% and 75% by treatment with aminoguanidine 25 mg/kg body weight starting from the day of streptozotocin injection (90). 2) Blocking AGE accumulation (measured by tissue fluorescence) in glomeruli and renal tubules in rats 32 weeks after induction of diabetes 32 weeks earlier; ponalrestat, an aldose reductase inhibitor, did not block AGE accumulation (91). Treatment of streptozotocin-induced diabetic rats with pimagidine prevents glomerular basement membrane thickening typical of renal morphologic changes noted in this model of diabetic nephropathy (92). 3) Reducing severity of experimental diabetic retinopathy as judged by a decrease in the number of acellular capillaries by 50% and complete prevention of arteriolar deposition of PAS-positive material and microthrombus formation after 26 weeks of induced diabetes in spontaneous hypertensive rats (93). 4) Ameliorating slowing of sciatic nerve conduction velocity dose dependently after treatment at three doses of 10, 25, and 50 mg/kg for 16 weeks (94). Autonomic neuropathy (neuroaxonal dystrophy), however, was not prevented by treatment with pimagidine (95). 5) Preventing development of the "stiff myocardium" that is a main component of diabetic cardiomyopathy (96). 6) Preventing the diabetes-induced 24% impairment in maximal endothelium-dependent relaxation to acetylcholine for phenylephrine precontracted aortas by treatment for 2 months in a dose of 1 g/kg/day (97). Blocking AGE formation to impede development of diabetic complications (98,99). is an attractive strategy because of elimination of the necessity for euglycemia (100).

Pimagidine treatment significantly prevents NO activation and limits tissue accumulation of AGEs. Corbett et al. speculate that pimagidine inhibits interleukin-1 beta-induced nitrite formation (an oxidation product of NO) (101). Uremia in diabetes is associated with both a high serum level of AGEs and accelerated macro and microvasculopathy. The renal clearance of AGE-peptides is 0.72 ± 0.23 ml/min for normal subjects and 0.61 ± 0.2 ml for diabetics with normal glomerular filtration (p value NS) (102). Diabetic uremic patients accumulate advanced glycosylated end-products in "toxic" amounts that are not decreased to normal by hemodialysis or peritoneal dialysis (103) but fall sharply, to within the normal range, within 8 hours of restoration of half-normal glomerular filtration by renal transplantation (104). It follows that the higher mortality of hemodialysis treated diabetic patients compared with those given a renal transplant may relate – in part – to persistent AGE toxicity.

Separate multicenter trials of aminoguanidine (Pimagidine) were conducted in adults with type I and type II diabetes and documented, fixed proteinuria of at least 500 mg/day, and a plasma creatinine concentration of <1.0 mg/dL (88 :mol/L) in women or <1.3 mg/dL (115 :mol/L) randomly assigned to treatment with aminoguanidine or placebo for four years. In the type 1 trial, reported in abstract, 56 sites enrolled 69 subjects randomized to receive 150 or 300 mg of aminoguanidine orally b.i.d. versus placebo with a mean treatment exposure of 2.5 years. Throughout the study, more than 90% of subjects in both treatment and placebo groups were concurrently treated with either an angiotensin converting enzyme inhibitor or receptor blocker. Compared with the placebo group, the aminoguanidine group evinced a significant (<0.05) reduction in doubling of serum creatinine concentration in those who had proteinuria >2g/24h. There was a nonsignificant "trend" toward slowing the creatinine rise in the entire group. Simultaneously, protection against diabetic retinopathy and a decrease in hyperlipidemia was noted in the treated group. Side effects in the aminoguanidine group included a transient flu-like syndrome, worsening anemia, and development of antinuclear autoantibodies (ANA) (105). A similar study in 599 subjects with type 2 diabetes enrolled in 84 centers in Canada and the US was interrupted because of liver function abnormalities in the aminoguanidine treated group. Other adverse effects of aminoguanidine treatment included myocardial infarction, congestive heart failure, atrial fibrillation, anemia, ANA titre conversion, and upper GI symptoms (106,107).

Other Agents

Although aminoguanidine inhibits initial stages of glycation in a hyperglycemic millieux, it only minimally blocks post-Amadori AGE formation. Other drugs, with promising activity against post-Amadori stages and/or effective breaking of crosslinks are underevaluation including desferrioxamine, D-penicillamine, pentoxifylline, pioglitazone, and metformin (108). ALT-946, another thiazolidine derivative AGE inhibitor, is more potent than aminoguanidine in inhibiting AGE-protein cross-linking (both in vitro and in vivo) (109). Compared with ALT-946 treated rats, albuminuria and AGE staining was twice as high in untreated diabetic rats, thereby providing a rationale for clinical trials in diabetic nephropathy (110).

At present, potential application of aminoguanidine (1827 Library of Medicine citations as of April 2003), related molecules, or AGE breakers remains a promise unfulfilled. Lessons learned from broad investigative experience with aminoguanidine center about the species differences between induced-diabetes in the rat, diabetes in the dog, and the human disease. While no further human trials of aminoguanidine have reached even the Phase 1 Trial stage, it is likely that AGEs will persist as a target for both prevention and amelioration of diabetic micro and macrovascular complications.

POST-TRANSPLANT DIABETES MELLITUS (PTDM)

Post-transplant diabetes mellitus (PTDM), a well-documented complication of tissue and organ transplantation was initially recognized in the steroid-azothioprine era with an incidence of 7-15% of patients (111,112). More potent immunosuppressive drugs, especially the calcineurin inhibitors cyclosporine and tacrolimus, increased allograft survival and decreased the dose of corticosteroid drugs but were associated with a higher incidence of PTDM (cyclosporine 3-6% (113,114,115,116), tacrolimus 15-32% (117)). Maes et al. hypothesized that the calceneurin inhibitors are diabetogenic (118). Data extracted from the USRDS show a cumulative incidence of PTDM at 3, 12 and 36 months of 9.1, 16 and 24% (119).

No clear understanding of the pathogenesis of PTDM is in hand. While steroid administration is linked to insulin resistance (120), both cyclosporine and tacrolimis may perturb carbohydrate metabolism by direct injury to pancreatic beta cell function resulting in diminished insulin synthesis or release (121,122,123), and decreased peripheral insulin sensitivity. Other, established risk factors for PTDM that may be additive to immunosuppressive drugs include race, older age, obesity, family history of diabetes, and certain HLA subtypes (124).

In the general population, both type 1 and type 2 diabetes are associated with extrarenal comorbid complications that shorten life. It has been suggested that PTDM is as prone to comorbid complications as non-transplant diabetes. In one study, renal allograft survival was significantly lower in PTDM patients at 12 years (48%) as compared with 70% in control patients, with no difference in patient survival (125). By contrast, the

Table 5. Comparison of ESRD options for diabetic patients

FACTOR	PERITONEAL DIALYSIS	HEMODIALYSIS	KIDNEY TRANSPLANT
Extensive extrarenal disease	No limitation	No limitation except for hypotension	Excluded in substantive cardiovascular insufficiency
Geriatric patients	No limitation	No limitation	Arbitrary age exclusion as determined by program
Complete rehabilitation	Rare, if ever	Very few individuals	Common so long as graft functions
Death rate	Much higher than for nondiabetics	Much higher than for nondiabetics	About the same as nondiabetics
First year survival	About 75-80%	About 75-80%	>90%
Survival to second decade	Almost never	Fewer than 5%	About 1 in 5
Progression of complications	Usual and unremitting. Hyperglycemia and hyperlipidemia accentuated.	Usual and unremitting. May benefit from metabolic control.	Interdicted by functioning pancreas + kidney. Partially ameliorated by correction of azotemia.
Special advantage	Can be self-performed. Avoids swings in solute and intravascular volume level.	Can be self-performed. Efficient extraction of solute and water in hours.	Cures uremia. Freedom to travel. Neuropathy, retinopathy may improve
Disadvantage	Peritonitis. Hyperinsulenemia, hyperglycemia, hyperlipidemia. Long hours of treatment. More days hospitalized than either hemodialysis or transplant.	Blood access a hazard for clotting, hemorrhage and infection. Cyclical hypotension, weakness. Aluminum toxicity, amyloidosis.	Cosmetic disfigurement, hypertension, personal expense for cytotoxic drugs. Induced malignancy. HIV transmission.
Patient acceptance	Variable, usual compliance with passive tolerance for regimen.	Variable, often noncompliant with dietary, metabolic, or antihypertensive component of regimen.	Enthusiastic during periods of good renal allograft function. Exalted when pancreas proffers euglycemia.
Bias in comparison	Delivered as first choice by enthusiasts though emerging evidence indicates substantially higher mortality than for hemodialysis.	Treatment by default. Often complicated by inattention to progressive cardiac and peripheral vascular disease.	All kidney transplant programs preselect those patients with fewest complications. Exclusion of those older than 45 for pancreas + kidney simultaneous grafting obviously favorably predjudices outcome.
Relative cost	Most expensive over long run	Less expensive than kidney transplant in first year, subsequent years more expensive.	Pancreas + kidney engraftment most expensive uremia therapy for diabetic. After first year, kidney transplant – alone – lowest cost option.

larger USRDS study (vide supra), including over 11,000 patients who received a first kidney transplant between 1996-2000, PTDM was associated with increased graft failure (RR 1.63, 1.46-1.84, $p < 0.0001$), death-censored graft failure (RR 1.46, 1.25-1.70, $p < 0.0001$), and mortality (RR 1.87, 1.60-2.18, $p < 0.0001$). Friedman et al.'s pre-cyclosporine era study (vide supra) found a 67% 2-year patient survival in transplant recipients with PTDM, compared with 83% survival in control patients. The USRDS analysis of 7092 nondiabetic recipients of first-kidney transplants between 1996 and 1998 who were followed for 3 years demonstrated a heightened risk of death (risk ratio 1.87) in those with PTDM. Cardiovascular disease, primarily acute myocardial infarction, is also the leading cause of death in renal transplant recipients with intact graft function (126), and PTDM probably contributes to this through the known atherosclerosis-promoting actions of hyperglycemia and hyperinsulinemia (127). In a 5-year follow-up study of 1347 renal transplant recipients with or without a functioning allograft, risk of death from ischemic heart disease was 20.8 times higher in transplanted diabetic patients, compared with a 6.4-fold higher risk in transplanted nondiabetic patients (128).

POST-TRANSPLANT LONG-TERM MANAGEMENT

Diabetic recipients of renal transplants spend more days during more frequent hospitalizations than do nondiabetic patients (129) for management of allograft failure, infections, peripheral vascular insufficiency or cardiac disease. Restoration of normal renal function in a diabetic with ESRD does not reverse concomitant advanced extrarenal micro- and macrovasculopathy. Starting with the immediate post-transplant period, management of the diabetic renal transplant recipient is often complex demanding attention from diverse subspecialists. In many instances, determining a single pathogenetic mechanism after interpretation of renal scans, sonograms, biopsies, and tests of glomerular and tubular function is still largely an art based on experience. The complex clinical judgements often required to restore euglycemia, baseline renal graft function and to treat infection in the setting of profound immunosuppression are best accomplished under the direction of transplant professionals, whether surgeons or nephrologists, with collaborating consultants involved as needed. Overall, survival of diabetic patients with ESRD has been improving annually over the past decade whether treated by peritoneal dialysis, hemodialysis, or a kidney transplant. Illustrating this point is the five year allograft function of 60.1% in diabetic cadaver kidney transplant recipients versus a five year allograft function of 60.3% of all recipients reported to the USRDS (1). This encouraging progress in therapy reflects multiple small advances in understanding of the pathogenesis of extrarenal micro- and macrovasculopathy in a previously inexorable disease, coupled with intensified regulation of hypertension and hyperglycemia. Identifying the perturbed biochemical reactions underlying the pathogenesis of diabetic vasculopathy − especially the adverse impact of accumulated advanced glycosylated end-products (AGEs) − raises the possibility of preempting end-organ damage without necessarily correcting hyperglycemia.

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