



## DIABETIC NEPHROPATHY: FRESH PERSPECTIVES

Eli A. Friedman

Renal Disease Division, Department of Medicine, State University of New York, Health Science Center at Brooklyn, Brooklyn, New York, USA

**Summary.** Diabetes is the disorder most often linked with development of end-stage renal disease (ESRD) in the USA, Europe, South America, Japan, India, and Africa. Kidney disease is as likely to develop in long-duration non-insulin dependent diabetes (type 2) as in insulin-dependent diabetes mellitus (type 1). Nephropathy in diabetes — if suboptimally managed — follows a predictable course starting with microalbuminuria through proteinuria, azotemia and culminating in ESRD. The rate of renal functional decline in diabetic nephropathy is slowed by normalization of hypertensive blood pressure, establishment of euglycemia, and a reduced dietary protein intake. When compared with other causes of ESRD, the diabetic patient sustains greater mortality and morbidity due to concomitant (co-morbid) systemic disorders especially coronary artery and cerebrovascular disease. A functioning kidney transplant provides the uremic diabetic patient better survival with superior rehabilitation than does either CAPD or maintenance hemodialysis. There are no reports, however, of prospective controlled studies of dialysis versus kidney transplantation in diabetic patients whose therapy was assigned randomly. For the minority (<10%) of diabetic ESRD patients who have, performance of a combined pancreas and kidney transplant may cure diabetes and permit full rehabilitation. No matter which ESRD therapy has been elected, optimal rehabilitation in diabetic ESRD patients requires that effort be devoted to recognition and management of co-morbid conditions.

Survival in treating ESRD in diabetes by dialytic therapy and renal transplantation is continuously improving. This inexorable progress in therapy reflects multiple small advances in understanding of the pathogenesis of extrarenal micro- and macrovasculopathy in an inexorable disease, coupled with safer immunosuppression. In this context, trials of pimagidine and aldose reductase inhibitors are now being conducted. Recognizing 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 blocking end-organ damage without necessarily correcting hyperglycemia.

**Key words:** Diabetes, epidemiology, dialysis, transplantation

### Introduction

End-stage renal disease (ESRD) registries in the United States (US), Japan, and most nations in industrialized Europe show that diabetes mellitus, in 1998, is the leading cause of renal failure world-wide. Glomerulonephritis and hypertensive renal disease have lower prevalence among new ESRD patients, substantiating Mauer and Chavers assertion that "Diabetes is the most important cause of ESRD in the Western world (1)." In every European and North American registry of renal failure patients, both the incidence and prevalence of diabetic patients has risen yearly over the past decade. Data from 1996, listed in the 1998 report of the United States Renal Data System (USRDS), underscore this point. Of 283,932 U.S. patients receiving either dialytic therapy or a kidney transplant in 1996, 92,211 had diabetes (2), a prevalence

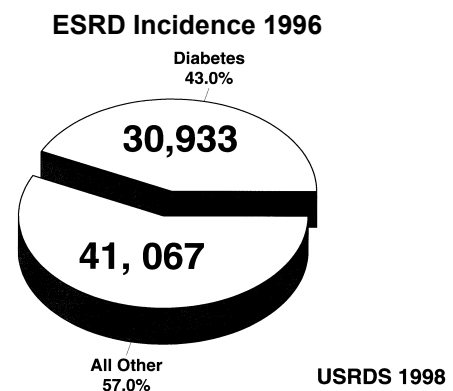


Fig. 1. Proportion of diabetic and nondiabetic incident ESRD patients in 1996 according to the United States Renal Data Systems Report of 1998. By the year 2000, diabetic ESRD patients may constitute one-half of all incident patients.

rate of 32.4%. During 1996, of 72,000 new (incident) cases of ESRD, 30,393 (43%) were listed as diabetic.

Nephrologists tend to relax metabolic and blood pressure control in diabetic patients once renal insufficiency progresses to ESRD. Their conviction that onset of irreversible uremia signals concurrent endpoints of other diabetic organopathies is incorrect. Indeed, the difference between acceptable functional rehabilitation and pathetic invalidism for diabetic ESRD patients hinges on provision of comprehensive extrarenal medical care. Additionally, both life quality and duration are linked to the choice of uremia therapy. Addressed herein are both the options open to the diabetic ESRD patient and the need for overall diabetic care during uremia therapy.

### Options for ESRD treatment in diabetes

As listed in Table 1, 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) no treatment, meaning passive suicide, is the choice more often selected for and by diabetic than by nondiabetic individuals. 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. As a consequence, CAPD may be the first choice in Toronto, home hemodialysis in Seattle, and a renal transplant in Minneapolis. No prospective, controlled trials of dialytic therapy — of any type — versus kidney transplantation have been reported. Therefore, what follows reflects an acknowledged bias in interpreting the bias of others.

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

Confusion over diabetes type is frequent when evaluating diabetic ESRD patients. Confounding diabetes type distinction is the realization 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 (3). Islet  $\beta$ -cell dysfunction in type 2 diabetes — including 56,059 with diabetes (27.2%) — varies with the different genetic defects associated with characteristic patterns of altered insulin secretion that can be defined clinically (4). Subjects with mild glucose intolerance and normal fasting glucose concentrations and normal glycosylated hemoglobin levels consistently manifest defective  $\beta$ -cell function, a component of type 2 diabetes that is present before onset of overt hyperglycemia. Hyperglycemia assessed by the level of hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) is the best predictor of microvascular and macrovascular complications of diabetes (5).

At the other extreme, it is well established that some patients with type 1 diabetes maintain a measurable level of pancreatic  $\beta$ -cell activity for many years after onset of the disease (6) thwarting the utility of C-peptide measurements to distinguish type 1 diabetes from type 2 diabetes (7).

Diabetes in America is predominantly type 2, fewer than eight 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* (8) in that: 1. The incidence (9) is higher in women, blacks (10), Hispanics (11), and native Americans (12). 2. The peak incidence of ESRD 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 United States, it is not surprising, therefore, that ESRD associated with diabetes is mainly a disease of poor, elderly blacks (13). By telephone survey of hemodialysis units in New York, Chicago, Oklahoma City, San Antonio and Detroit, I determined that one-third to more than one-half of newly diagnosed *inner city* ESRD patients starting maintenance hemodialysis are diabetic black or Hispanic persons — predominantly women — over the age of 50.

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 (14, 15). 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 (16). While there are differences between type 1 diabetes and type 2 diabetes in genetic predisposition (17) and racial expression, other aspects of the two disorders - particularly manifestations of nephropathy - are remarkably similar.

Careful observation of the course of nephropathy in type 1 and type 2 diabetes indicates strong similarities in rate of renal functional deterioration (18) 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

(19). Not yet included in USRDS reports is any distinction between type 1 and type 2 diabetes in terms of dialysis morbidity and mortality or posttransplant patient and allograft survival.

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 (20, 21). 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. Sadly, depression caused by multiple complications during dialytic therapy prompts a substantially higher rate of withdrawal from therapy (suicide) in diabetic than in nondiabetic ESRD patients.

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

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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.
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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 who begin maintenance dialysis or receive a renal allograft have undergone laser treatment and/or vitrectomy for retinopathy. We routinely collaborate with an ophthalmologist skilled in retinal disorders. By this tact, laser and/or vitreous surgery can be integrated as a component of comprehensive management (22). Similarly, we consult — even in asymptomatic patients — a cardiologist familiar with uremia in diabetic

patients. Coronary angiography (if indicated), is performed as a valuable maneuver to detect those for whom prophylactic coronary artery angioplasty or bypass surgery is likely to extend life. Included on our renal team is a podiatrist who delivers routine foot care. The podiatrist has by regular surveillance of patients at risk of major lower extremity disease sharply reduced the chance 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. Gastroparesis afflicts one-quarter to one-half of azotemic diabetic persons when initially evaluated for renal disease (23). Other expressions of autonomic neuropathy — obstipation and explosive nighttime diarrhea — often coexists with gastroparesis (24). Obstipation responds to daily doses of cascara, while diarrhea is treated with psyllium seed dietary supplements one to three times daily plus loperamide (25) in repetitive 2 mg. doses to a total dose of 18 mg daily.

Pregnancy in a diabetics with proteinuria or azotemia, previously regarded as an unavoidable prelude to disaster — in terms of fetal loss and/or maternal risk of death — is now managed with a high probability of successful outcome. Miodovnik et al. followed 182 pregnant women with type 1 diabetes, 46 of whom had overt nephropathy for a minimum of 3 years after delivery and concluded that pregnancy neither increases the risk of subsequent nephropathy nor accelerates progression of preexisting renal disease (26). In an equally encouraging series from Finland, Kaaja et al. followed 28 diabetic women for 7 years after delivery compared with 17 nulliparous controls matched for age, duration of diabetes, and severity of vasculopathy and concluded that: "pregnancy does not seem to affect development or progression of diabetic nephropathy (27)."

### 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. Diabetic ESRD patients select the no further treatment option, equivalent to passive suicide, more frequently than do nondiabetic patients (28). 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 (29).

Unfortunately, in both Europe and the US, so called "preterminal care in diabetic patients with ESRD" is deficient in amount and quality (30) with inadequate attention to control of hypertension, hyperlipidemia or ophthalmologic intervention (31). For the large majority — over 80% of diabetic persons who develop ESRD in the United States — 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 (32). 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 (33). Approximately 50% of diabetic patients begun on maintenance hemodialysis die within two years of their first dialysis.

### Peritoneal dialysis

In the U.S., 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 (34). To permit CAPD, an intraperitoneal catheter is implanted one or more days before CAPD is begun. Even blind diabetic patients learn to perform CAPD at home within 10 to 30 days. 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 (35). A less enthusiastic 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 (36). 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 (37)."

### Kidney transplantation

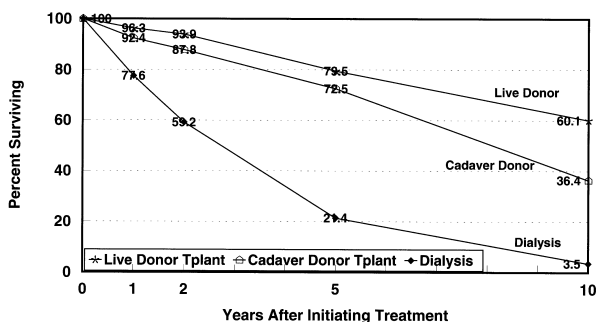
As predicted by Sutherland et al. (38), following a renal transplant, patient survival at one and two years is now equivalent in diabetic and nondiabetic recipients (39), though graft survival, in some large series, remains marginally lower in diabetic persons. At its best, as illustrated by a single center retrospective review of all kidney transplants performed between 1987 and 1993, there is no significant difference in actuarial 5-year patient or kidney graft survival between diabetic and nondiabetic recipients overall or when analyzed by donor source. Furthermore, no difference in mean serum creatinine levels at 5 years was discerned between diabetic and nondiabetic recipients (40). Statistical superiority in survival after a renal transplant, compared with dialytic therapy, does not tell the whole story as rehabilitation is incomparably better. The enhanced life quality effected prompts selection of a kidney transplant as the distinctly favored treatment presented to newly evaluated diabetic persons with ESRD under the age of 60. More than half of diabetic kidney transplant recipients in most series live for at least three years: many survivors return to occupational, school and home responsibilities.

Positioning the option of a combined pancreas and kidney transplant for the diabetic ESRD patient is presently difficult. Though still regarded as investigational by some (41) and, even when successful, applicable to no more than 9% of uremic diabetic patients who have type 1 diabetes, pancreatic transplantation is growing in acceptability and technical success (42) In one remark-

able series, survival one year post-renal transplant, in 995 diabetic kidney recipients who also received a pancreas transplant renal allograft survival was a remarkable 84% (43). World-wide results in simultaneous kidney-pancreas transplants show that more than 90% of recipients were alive at 1 year, more than 80% had functioning kidney grafts, and more than 70% no longer required insulin (44).

Combining pancreas and kidney transplants does not raise perioperative mortality; but perioperative morbidity is greatly increased, mainly due to mechanical and inflammatory problems diverting pancreatic exocrine secretions into the urinary system. When restricted to type 1 recipients younger than 45 years old, as reported by the University of Texas, a simultaneous pancreas and kidney transplant permits a five year patient survival of 78% with kidney and pancreas function at five years of 69% and 62% respectively (45). By sharp contrast, however, the pioneer series of pancreas transplants at the University of Minnesota had a three year patient survival in 54 patients given a simultaneous kidney and pancreas transplant of only 68% versus a 90% survival in 46 patients given a cadaver kidney alone (46).

### Survival of Diabetic ESRD Patients



USRDS 1998

Fig. 2. Progressive improvement in diabetic ESRD patients treated by hemodialysis or cadaver renal transplantation is evident over the past decade. Data are from the United States Renal Data Systems Report of 1998.

A great expectation for pancreatic transplantation, is interdiction of diabetic micro- and macrovascular extrarenal complications. Several reports of kidney biopsies in patients who have received sequential kidney and later pancreas allografts indicate that a functioning pancreas does impede progression or recurrence of diabetic nephropathy. Likewise, the course of diabetic neuropathy following combined pancreas and kidney transplantation underscores stabilization and, in some patients, improvement in diabetic motor neuropathy (47). Unfortunately, pancreas transplantation in patients with extensive extrarenal disease, has neither arrested nor reversed diabetic retinopathy, diabetic cardiomyopathy, or extensive peripheral vascular disease (48, 49). Nevertheless, a

functioning pancreas transplant does free patients with type 1 diabetes from the dreaded daily sentence of balancing diet, exercise, and insulin dosage (50). In 1998, consensus of clinical nephrologists is that the ESRD patient with type 1 diabetes should consider a simultaneous kidney and pancreas transplant as at least a temporary cure of inexorable disease (51).

### Patient survival during treatment of ESRD

All reported comparisons (retrospective and prospective) of the fate of diabetic patients treated for ESRD by different modalities lack balanced treatment groups in terms of equalities in age, race, diabetes type, severity of complications, and degree of metabolic control. 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 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 (52)." 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.

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 (53). 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 (54).

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 (55). 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 (56). 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). 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 57% in diabetic cadaver kidney transplant recipients versus a five year allograft function of 58% of all recipients reported to the USRDS (57).

## 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. 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. 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 United States, 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, 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 (58) was employed to assess patient well being (59). 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.

### Improving prognosis: Diabetic ESRD Patients

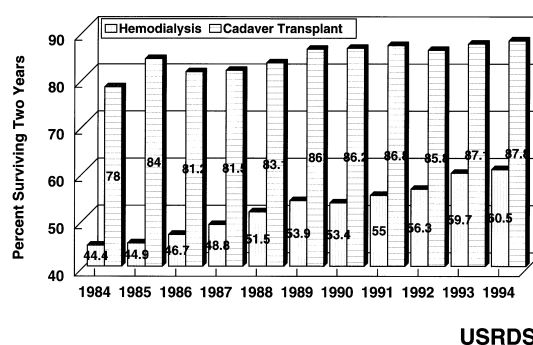


Fig. 3. Renal transplantation from a live donor affords the best long term survival to diabetic ESRD patients. The dismal outcome for dialysis patients plots the combined peritoneal dialysis and hemodialysis subsets. Data are from the United States Renal Data Systems Report of 1998.

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 (60). 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<sup>23</sup>. 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 (61), and elderly inner-city (62) hemodialysis patients. The inescapable conclusion of studies to date is that maintenance hemodialysis — in many instances — does not permit return to life's responsibilities for diabetic individuals.

Table 3. 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 cardiovascular Insufficiency
Geriatric patients	No limitation	No limitation	Arbitrary 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%	About 75%	>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.
Disadvantage	Peritonitis. Hyperinsulinemia, 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 prejudices 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.

## 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 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. Variables in morbidity in diabetic kidney transplant recipients the 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 access-site 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

## Pre-ESRD intervention

Screening for microalbuminuria should be performed annually and a spot urine albumin:creatinine ratio should be calculated to identify those diabetics at risk for nephropathy, retinopathy, and cardiovascular disease according to 1995 recommendations of the National Kidney Foundation (63). Once such high-risk individuals are noted, treatment with an angiotensin-converting enzyme (ACE) inhibitor should be started. Ravid et al. in a double-blinded randomized control study of 94 normotensive type 2 diabetes patients with microalbuminuria treated with enalapril for 7 years reported that the drug stabilizes renal function with an "absolute risk reduction of 42% for nephropathy (64)." Other signs have been proposed for risk factors of renal deterioration. For example, a prolonged QT interval in a standard 12-lead electrocardiogram was a predictor of

an increased risk of death in 85 proteinuric type 1 diabetes patients followed for 5-13 years (65). For the present, however, microalbuminuria and hypertension are the most reliable indicators of impending renal failure.

As reviewed by Nathan (66), both nephropathy and retinopathy are delayed in onset by a regimen termed *intensive therapy of diabetes* which consists of striving for euglycemia (tight control), dietary protein restriction, and blood pressure reduction. Sustained euglycemia reduces enlarged kidney size typical of early hyperfiltration (67). Prevention of the synthesis of sorbitol and other alcohols by inhibition of aldose reductase interdicts nephropathy, neuropathy and retinopathy in rats, an approach that may be applicable to human diabetes (68). Intensive attention to striving for euglycemia reduces the cumulative incidence and overall risk for development of microalbuminuria as well as clinical albuminuria (defined as  $\geq 208 \mu\text{g}/\text{min}$ ), a derivative finding in the Diabetes Control and Complications Trial (DCCT) (69). Another strategy retarding diabetic microvasculopathy — in trial in Spain and Russia — is a reduction in erythrocyte stiffness, a hemorrheological alteration universally noted in diabetes, by administration of pentoxifylline (70, 71) in type 1 diabetes and type 2 diabetes.

Hypertension is a major confounding factor in the genesis and progression of nephropathy. In hypertensive subjects with type 2 diabetes >10 years, 36% had impaired renal function defined as a glomerular filtration rate  $< 80 \text{ ml}/\text{min}/1.73 \text{ m}^2$  or a serum creatinine concentration  $> 1.4 \text{ mg}/\text{dl}$  and 75% had microalbuminuria or clinical proteinuria (72). Control of hypertension (73) — increasingly by angiotensin-converting enzyme inhibition (74) — and hyperglycemia (75) are the main components of contemporary treatment. It is now clear that use of an ACE inhibitor proffers unique benefit to halting progression of both microalbuminuria and proteinuria or in diabetic patients (76). Studies with beta-blockers, calcium antagonists, diuretics, and AGE inhibitors in hypertensive diabetics with microalbuminuria have all shown significant reduction in urinary albumin excretion rates. When applied as monotherapy for 12 weeks in 31 diabetic patients with established microalbuminuria, captopril and indapamide were equivalent in blood pressure reduction and decrease of proteinuria (77). Depending on the choice of calcium antagonist, sodium intake may modulate reduction of albumin excretion; diltiazem which decreased proteinuria in patients fed a diet containing 50 mEq/day of sodium was ineffective in reducing proteinuria when sodium intake was increased to 250 mEq/day while nifedipine decreased proteinuria independent of dietary sodium intake (78). Treatment with captopril, an ACE inhibitor administered for 18 months to 24 type 2 diabetes patients with proteinuria  $> 500 \text{ mg}/\text{day}$  reduced proteinuria and prevented decrease in GFR compared with 18 type 2 diabetes treated with "conventional" antihypertensive drugs (79). Recently, the renal protective



effects of ACE inhibitors have been extended to reducing proteinuria, limiting GFR decline, and preventing ESRD in proteinuric, nondiabetic renal disorders except for polycystic kidney disease (80).

Smoking cigarettes increases systolic blood pressure and proteinuria in both micro- and macroalbuminuric type 1 diabetes patients and should be counted as a risk for faster progression of diabetic nephropathy (81). Wang, Lau, and Chalmers conducted a meta-analysis of the effects of intensive blood glucose control on the development of late complications of type 1 diabetes concluding that "Long-term intensive blood glucose control significantly reduces the risk of diabetic retinopathy and nephropathy progression (82)." Dietary protein restriction, previously thought to be beneficial in retarding loss of renal function (83) was ineffective in a prospective multicenter trial in nondiabetic patients in Italy. Furthermore, in type 2 diabetes, dietary protein intake does not correlate with the degree of proteinuria (84). By contrast, in a meta-analysis of five randomized, controlled or time-controlled with nonrandomized crossover design studies comprising 108 patients with type 1 diabetes with a mean follow-up of 9 to 35 months, "a low-protein diet significantly slowed the increase in urinary albumin level or the decline in glomerular filtration rate or creatinine clearance (85)." By consensus, most nephrologists now advise limitation in dietary protein in the belief that the rate of deterioration of renal function will be slowed.

There are no data supporting 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  $\geq 2.5$  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 (86). 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 an increase in severity of hypertension as red cell mass increases is based in the finding that ambulatory maintenance hemodialysis patients evince such a change (87). 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).

A *Life Plan* 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 choose 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 which culminates in passive suicide.

#### *Future Directions of Therapy*

Perturbed micro- and macrovascular function is strongly implicated in the cellular and molecular abnormalities of vascular endothelium in diabetes (88). Hyperglycemia is increasingly linked to the pathogenesis of nephropathy, retinopathy, and atherosclerosis in individuals with long-duration diabetes (89). The metabolic pathway between a high ambient glucose concentration and end organ damage in diabetes is under intensive investigation. Three candidate mechanisms are (90): 1. activation of the aldose-reductase pathway leading to toxic accumulation of sorbitol in nerves; 2. accelerated nonenzymatic glycosylation with deposition of advanced glycosylated endproducts (91); 3. activation of isoform(s) of protein kinase C in vascular tissue initiating a cascade of events culminating in diabetic complications (91). PKC activity is increased in renal glomeruli, retina, aorta, and heart of diabetic animals, probably because of increased synthesis de novo of diacylglycerol (DAG), a major endogenous activator of PKC (93).

#### *PKC in Diabetic Complications*

Vascular damage in diabetes develops slowly over years to decades in the presence of continuous hyperglycemia (94). Sustained alterations in PKC-regulated gene expression in vascular cells may contribute to the onset and progression of vascular abnormalities in diabetes. Activation of PKC begins a complex network of intracellular signaling that could change gene expression (95). A result of altered gene expression might be changed transcription factor binding to promoter regions on responsive genes as for example, the collagenase gene promoter that responds to

the PKC agonist, phorbol ester, by binding both AP-1 and PEA3 transcription factor proteins (96).

A role for PKC in the pathogenesis of diabetic nephropathy is inferred from experiments in induced-diabetic rats. Evidence for this linkage includes findings that: 1. PKC is activated in glomeruli isolated from diabetic rats (97). 2. Activation of PKC by either intravitreal injection of the PKC agonist, phorbol 12,13-dibutyrate (98) or by exposure of granulation tissue to the PKC agonist, 12-O-tetradecanoylphorbol3-acetate in normal rats reproduces the vascular abnormalities induced by diabetes and high glucose levels (99). 3. Mesangial cells cultured in high (27.8 mM) concentration of glucose for 5 days increase PKC and mitogen-activated protein kinase activity in their membrane fraction supporting the hypothesis that hyperglycemia induces abnormalities in the glomerular mesangium (100). Furthermore, PKC promotes elevated levels of mRNA encoding matrix components— matrix synthesis is accelerated in early diabetic glomerulopathy — in glomeruli isolated from streptozotocin-induced diabetic rats (101). The metalion vanadate, advocated in human diabetes for its insulin-like effects, undesirably also stimulates PKC activity in human mesangial cells in vitro thereby limiting its application in clinical trials (102).

#### *Inhibitors of PKC*

A small synthetic organic molecule belonging to the class of naphthopyrans, 2-amino-4-(3-nitrophenyl)-4H-naphtho(1,2-B)-pyran-3-carbonitrile (LY290181) when applied topically (20-50  $\mu$ mol/l) to newly grown vessels in granulation tissue, blocked glucose-induced increases in both blood flow and permeability. Additionally, when included as 0.1% of the diet for 8 weeks in male Sprague-Dawley streptozotocin-induced diabetic rats, LY290181 prevented diabetes-induced increases in albumin permeation in the retina, nerve, and aorta, but did not effect albumin permeation in muscle or brain. Because LY290181 inhibited phorbol ester-stimulated activation of the porcine urokinase plasminogen activator (uPA) promoter (-4600/+398 linked to the chloramphenicol acetyltransferase (CAT) reporter gene (p4660CAT), it was inferred that this unique chemical may block diabetes-induced vascular dysfunction by inhibiting transcription factor binding to specific PKC-regulated genes involved in vascular function (103).

Based on the observation that it is the PKC  $\beta_2$  isoenzyme that is preferentially activated in the retina, heart, and aorta of diabetic rats [6] an orally effective inhibitor of PKC  $\beta_2$  was synthesized and found to ameliorate vascular dysfunction in streptozotocin-induced diabetic rats (104). The macrocyclic bis(indolyl)maleimide structure (LY333531) selectively inhibits PKC  $\beta$ . LY333531 corrected renal functional perturbations in diabetic rats but had no effect on renal function in normal rats. GFR was  $3.0 \pm 0.2$  ml/min in nondiabetic rats, increased to  $4.6 \pm 0.4$  ml/min in diabetic rats, and returned to normal after oral treatment

with LY333531 (1.0 and 10 mg/dk) for 8 weeks. Concomitantly, urinary albumin excretion rate was decreased in diabetic rats treated with LY333531 from  $11.7 \pm 0.5$  mg/day to  $4.9 \pm 1.6$  mg/day (normal  $1.6 \pm 0.5$  mg/day). No change in glycosylated hemoglobin or DAG content in the retina or glomeruli of diabetic rats resulted from treatment with LY333531. These early trials of PKC inhibition underscore potential treatment of diabetes with pharmaceutical agents that block organ damage due to hyperglycemia without the requirement for euglycemia. The fact that no adverse reactions followed 8 weeks of oral administration in rats is an encouraging first step along the long road that may culminate in clinical trials.

### **Aldose reductase and sorbitol**

The role of the sorbitol pathway in diabetic complications has been termed "the longest running controversy among researchers and clinicians studying this disease (105)." The *polyol/sorbitol hypothesis* is an attractive explanation for the mechanism by which hyperglycemia induces diabetic complications because it raises the therapeutic possibility of preventing injury by blocking a biochemical pathway without the necessity for establishing often difficult to attain euglycemia. The finding of excess sorbitol in cataracts in diabetic rats (106), stimulated the hypothesis that high ambient glucose levels damage cells by increasing intracellular osmolality, decreasing myoinositol levels thereby altering Na<sup>+</sup>/K<sup>+</sup> ATPase activity ( nerves) or shifting redox potential in cells. Aldose reductase, an enzyme present in most tissues, converts glucose to sorbitol, which is further processed to fructose. The enzyme has a low affinity for glucose, and under physiologic conditions little substrate is processed. In experimental diabetes, sorbitol production is markedly enhanced by hyperglycemia leading to its accumulation and injury to cells (107). type 2 diabetes patients with either proliferative or nonproliferative retinopathy have significantly higher levels of erythrocyte aldose reductase than do type 2 diabetes patients without retinopathy despite equivalent mean HBA1c and blood pressure levels. On the other hand, erythrocyte aldose reductase activity in type 2 diabetes patients is not correlated with age, duration of diabetes, fasting blood glucose or HbA1c (108).

Drugs which block aldose reductase activity include spirohydantoin (sorbitol), carboxylic acid derivatives (tolrestat and ponalrestat), and flavonoids. Clinical trials over the past decade have assessed the efficacy of sorbinil, tolrestat, and ponalrestat in the treatment of diabetic retinopathy, neuropathy, and nephropathy. Overall, though some positive results have been reported, the benefits have been minimal and of no clinical moment. Due to its severe and frequent toxicity, sorbinil has been withdrawn from further use. Ponalrestat has not been effective in clinical trials.

Disappointment over the unfulfilled promise of aldose reductase inhibitors may reflect selection of too low a drug study dose in anticipation of toxic reactions at higher doses and/or insufficient duration of study. From the DCCT it is evident that the complications of diabetes develop slowly, often taking a decade or longer to become evident clinically. Therefore, drug evaluations in the early stages of nephropathy, neuropathy, and retinopathy may not be detect statistically different differences between treatment groups for years. Large scale, long-term drug trials in a slowly evolving disorder such as diabetic vasculopathy are difficult to design and expensive to conduct. Presently, tolrestat is the only aldose reductase inhibitor being tested in the U.S., in a multicenter trial for diabetic nephropathy, neuropathy, and retinopathy.

### Advanced glycosylated endproducts

In health, protein alteration resulting from a nonenzymatic reaction between ambient glucose and primary amino groups on proteins to form glycosylated 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 (109). Accumulation of AGEs in the human body is implicated in aging and in complications of renal failure (110) and diabetes (111). 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 (112).

Glomerular hyperfiltration, characteristic of the clinically silent early phase of diabetic nephropathy may be induced by Amadori protein products — in rats, infusion of glycosylated serum proteins induces glomerular hyperfiltration (113). Nitric oxide, produced by endothelial cells, the most powerful vasodilator influencing glomerular hemodynamics (114), has enhanced activity in early experimental diabetes (115). Subsequently, AGEs, by quenching nitric oxide synthase activity, limit vasodilation and reduce glomerular filtration rate (116). 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.

#### *AGEs in atherosclerosis*

An additional avenue of AGE research concerns their potential to promote rapidly progressive athero-

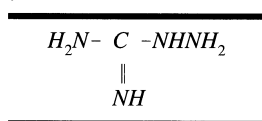
sclerosis in patients with diabetes and renal insufficiency. The azotemic diabetic manifests elevation in the plasma level of apoprotein B (ApoB), very low density lipoprotein (VLDL) and low density lipoprotein (LDL). Under this circumstance, circulating high levels of AGEs react directly with plasma lipoproteins preventing their recognition by tissue LDL receptors significantly increasing the level of AGE-modified LDL in the plasma of diabetic or nondiabetic uremic patients compared with normal controls, possibly contributing to the accelerated atherosclerosis that is typical of diabetes and uremia (117). LDL modified *in vitro* by AGE-peptides to the level present in azotemic diabetic patients markedly impaired LDL clearance kinetics when injected into transgenic mice expressing the human LDL receptor indicating that AGE modification of LDL receptors promotes elevated LDL levels in azotemic diabetic patients. Immunohistochemical analysis of coronary arteries obtained from type 2 diabetes patients stained with anti-AGE antibodies showed high levels of AGE reactivity within atherosclerotic plaques (118). From these observations, a linkage between hyperglycemia, hyperlipidemia, nitric oxide activity, and atherosclerosis in diabetes becomes obvious. Central to all this pathologic processes is the primary event of hyperglycemia.

AGE formation probably also contributes to development of diabetic complications by changing the structure and function of extracellular matrix in the glomerular mesangium and elsewhere. When segregated by type, it has been noted that on the surface of type IV collagen from basement membrane, AGE formation decreases binding of the noncollagenous NC1 domain to the helix-rich domain, interfering with the lateral association of these molecules into a normal lattice structure (119). By contrast, denaturation of type I collagen, a substance also found in glomerular mesangium, by AGEs expands molecular packing (120). Changing the integrity of collagen adversely affects biological functions important to normal vascular tissue integrity such as reaction to endothelium-derived relaxing factor (nitric oxide) and antiproliferative factor (17). In this context, as cited above, studies in rodents suggest that AGEs exert their toxicity by impairing nitric oxide-mediated vital processes including neurotransmission (121), wound healing (122) and blood flow in small vessels (123). Thus, AGEs by blocking the synthesis of nitric oxide, almost certainly interfere with maintenance of normal physiologic processes such as autoregulation of blood flow (124). The myriad actions of nitric oxide pertinent to nephrologists have been recently reviewed journal (125).

**Pimagidine** — 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 (126) and

reduces measured AGE levels leading to its investigation as a potential treatment. Pimagidine was selected because its structure is similar to  $\alpha$ -hydrazinohistidine, a compound known to reduce diabetes-induced vascular leakage, while having opposite effects on histamine levels (127).

Pimagidine treatment in rats made diabetic with streptozotocin preempts complications viewed as surrogates for human diabetic complications. Representative examples from the recent 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 (128). 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 (129). 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 (130). 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 (131). 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 (132). Autonomic neuropathy (neuroaxonal dystrophy), however, was not prevented by treatment with pimagidine (133). 5) Preventing development of the "stiff myocardium" that is a main component of diabetic cardiomyopathy; in a dose of 7.35 mmol/kg/dl for 4 months, aminoguanidine prevented both increased myocardial collagen fluorescence indicative of AGE accumulation and decreased left ventricular end-diastolic compliance characteristic of early cardiomyopathy (134). 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 (135). The strategic potential of blocking AGE formation to impede development of diabetic complications has been reviewed (136, 137). An attractive aspect of this approach to impeding diabetic complications is the elimination of the necessity for euglycemia (138).



**Aminoguanidine (Pimagidine) Empirical formula:**  
**CH<sub>6</sub>N<sub>4</sub> Molecular weight: 110.5**

Neither animal models of pancreatic beta cell toxicity-induced diabetes (139, 140, 141, 142) nor inbred spontaneous rodent strains with sustained hyperglycemia emulate the sequential intraglomerular hyperfiltration, glomerulopathy and renal insufficiency of human diabetic nephropathy (143). In normal rats, however, daily injection of AGE-modified rat albumin 25 mg per kg per day i.v. induced both albuminuria and glomerulosclerosis — perturbations characteristic of diabetic nephropathy (144). The nephropathy was AGE-specific as treatment with pimagidine ameliorated its severity.

**Mechanism of pimagidine action** — 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) (145). In a derivative study, pimagidine but not methylguanidine, inhibited AGE formation from L-lysine and G6P while both guanidine compounds were equally effective in normalizing albumin permeation in induced-diabetic rats (146). A role for a relative or absolute increase in NO production in the pathogenesis of early diabetic vascular dysfunction was also inferred as was the possibility that inhibition of diabetic vascular functional changes by pimagidine may reflect inhibition of NO synthase activity rather than, or in addition to, prevention of AGE formation. An alternative role assigned to pimagidine is that of a glucose competitor for the same protein-to-protein bond (147) that becomes the link for the formation and accumulation of irreversible and highly reactive advanced glycation end-products (AGE) over long-lived fundamental molecules such as the constituents of arterial wall collagen, GBM, nerve myelin, DNA and others. The mechanism by which pimagidine prevents renal, eye, nerve, and other microvascular complications in animal models of diabetes is under investigation (148). Separate multicenter clinical trials of pimagidine in type 1 diabetes and type 2 diabetes whose proteinuria is attributable to diabetic nephropathy are in progress. Adults with documented diabetes, fixed proteinuria  $\geq 500$  mg/day and a serum creatinine concentration  $\geq 1.2$  mg/dl for women and  $\geq 1.5$  mg/dl for men, will be randomly assigned to treatment with pimagidine or a placebo for four years. The effect of treatment on the amount of proteinuria, progression of renal insufficiency, and the course of retinopathy will be monitored.

**AGEs in renal failure** — 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  $0.72 \pm 0.23$  ml/min for normal subjects and  $0.61 \pm 0.2$  ml for diabetics with normal glomerular filtration (p value NS) (149). Diabetic uremic patients accumulate advanced glycosylated end-products in "toxic" amounts that are not decreased to normal by hemodialysis or peritoneal dialysis (150) but fall sharply, to within the normal

range, within 8 hours of restoration of half-normal glomerular filtration by renal transplantation (151). 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. A trial of pimagidine in diabetic hemodialysis patients begun in 1996 is designed to test this hypothesis.

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## DIJABETESNA NEFROPATIJA: PERSPEKTIVE

*Eli A. Friedman*

*Renal Disease Division, Department of Medicine, State University of New York, Health Science Center at Brooklyn, Brooklyn, New York, USA*

Kratak sadržaj: *U SAD, Evropi, Južnoj Americi, Japanu, Indiji i Africi dijabetes je najčešći uzrok terminalne hronične bubrežne insuficijencije (THBI). Bubrežno oboljenje se javlja posle više godina trajanja insulin-nezavisnog dijabetesa (tip 2), kao i insulin-zavisnog dijabetesa (tip 1). Nefropatija u dijabetesu – ako nije adekvatno lečena – razvija se*



*određenim tokom tako što počinje sa mikroalbuminurijom preko proteinurije, azotemije i završava se sa THBI. Stepem propadanja bubrežne funkcije usporava se kontrolom krvnog pritiska, glikemije i smanjenim unosom proteina. U poređenju sa drugim bolesnicima u THBI, dijabetesni bolesnik ima veći morbiditet i mortalitet, zbog istovremeno prisutnih (ko-morbidnih) sistemskih poremećaja, posebno koronarnog i cerebrovaskularnog oboljenja. Funkcionalni kalem bubrega omogućuje dijabetesnom uremičnom bolesniku bolje preživljavanje sa boljom rehabilitacijom, nego što to omogućuje CAPD ili trajna hemodijaliza. Međutim, nema prospektivnih kontrolisanih studija odnosa dijalize i transplantacije bubrega sa raspodelom bolesnika u grupe slučajnim izborom. Za manji broj (<10%) dijabetesnih bolesnika u THBI kombinovani kalem bubrega i pankreasa može da izleči dijabetes i omogući potpunu rehabilitaciju. No, bez obzira na izbor načina lečenja THBI, optimalna rehabilitacija zahteva napor da se prepoznaju i leče ko-morbidni poremećaji.*

*Preživljavanje dijabetesnih bolesnika sa THBI na dijalizi i sa presađenim bubregom se neprekidno popravlja. Neumitni napredak u lečenju odražava brojne manje pomake u razumevanju patogeneze mikro- i makrovaskularnih poremećaja, povezano sa sigurnijom imunosupresijom. Prepoznavanjem poremećenih biohemijskih procesa koji se nalaze u osnovi patogeneze dijabetičke vaskulopatije, posebno nepovoljan uticaj nagomilanih krajnjih produkata glikozilacije, otvara se mogućnost za prevenciju oštećenja pojedinih organa bez neophodne korekcije hiperglikemije.*

*Ključne reči: Dijabetes, epidemiologija, dijaliza, transplantacija*

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