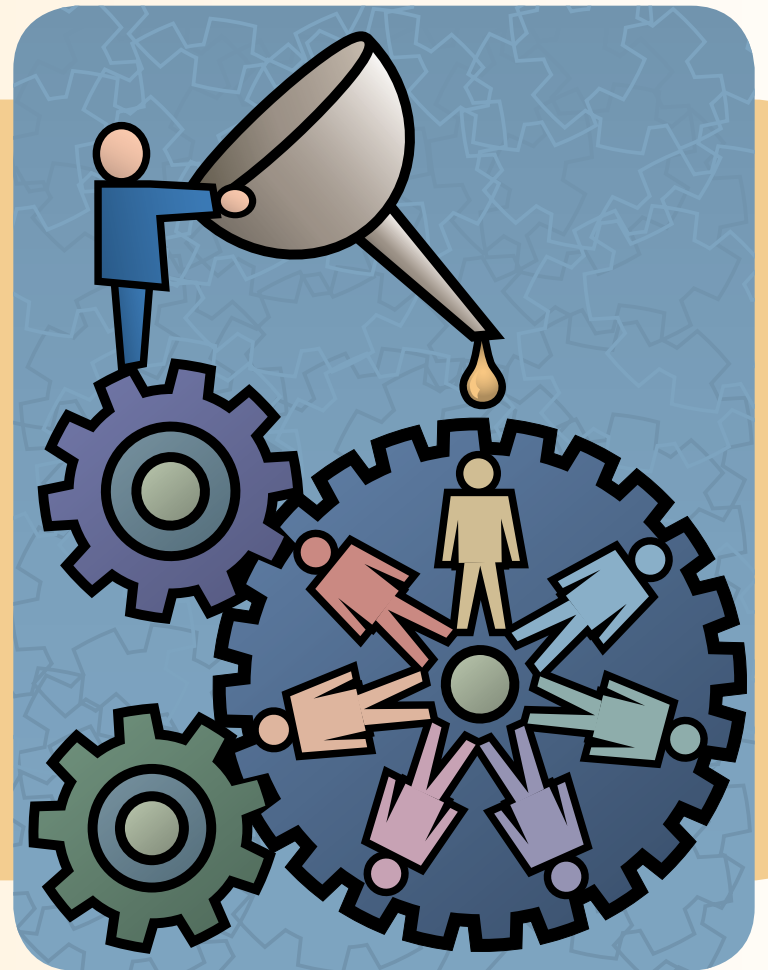


Diabetic Nephropathy

The impact of diabetic kidney disease on the health of the U.S. population is staggering. More than 23 million Americans have diabetes, which is the leading cause of chronic kidney disease and end stage renal disease in this country.

In this issue, we review our current understanding of the physiologic, epidemiologic, and genetic factors that influence the pathogenesis and susceptibility to the early stages of tissue injury related to diabetes. Also discussed are the goals of conservative therapy in patients with established diabetic kidney disease and a review of the principles related to dialysis modality selection for those with advanced disease requiring renal replacement therapy. Finally, we review the issues and challenges of managing new-onset diabetes after kidney transplantation and other solid organ transplant groups of patients.

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Does dialysis modality matter in diabetic patients with end stage renal disease?

By Anjali Bhatt Saxena and Rajnish Mehrotra

By the end of 2007, over 500,000 Americans were afflicted with end stage renal disease (ESRD), and almost 368,000 patients were undergoing dialysis therapy. Diabetes remains the most common cause of ESRD and accounts for over one-half of all new dialysis patients in the United States. Diabetic dialysis patients have poorer outcomes in general compared to nondiabetics. As a result, clinicians and researchers alike are searching for ways to improve outcomes of these patients.

The basic question of whether dialysis modality *per se* affects the survival of ESRD patients has been debated since the introduction of peritoneal dialysis (PD) for the treatment of ESRD. This issue is particularly important for diabetics because several observational studies have shown a higher risk for death among older diabetic patients treated with PD. Indeed, based on the results of some observational studies, some have questioned whether it is ethical to offer PD as an option for older diabetics.

There are many theoretical advantages and disadvantages to both hemodialysis (HD) and PD (Table 1). Special consideration should be given to diabetics with ESRD since these patients have more severe vascular disease and a higher risk for

infection than their nondiabetic counterparts. For diabetics with ESRD, PD may provide certain advantages over HD (Table 2). On the other hand, valid concerns about the adverse effects of glucose-based peritoneal dialysis solutions, including the risks of weight gain and worsened hyperglycemia, may limit PD utilization in diabetics.

Many researchers have sought to answer the question of which dialysis modality is superior. A randomized controlled trial (RCT) would most reliably examine whether any differences in outcomes of patients treated with HD or PD are attributable to the dialysis modality *per se*, but the existing body of literature is unfortunately lacking in RCTs. The Netherlands Cooperative Study of Dialysis (NECOSAD) is the most recent attempt to perform such an RCT. In this study, 735 of 773 eligible patients refused to be randomized to either HD or PD, thus leaving a study group of only 38 patients—far too few from which to make meaningful conclusions. In the absence of RCTs, data examining the effects of dialysis modality are limited to those originating from either observational or prospective cohort studies.

The observational studies examining

survival differences between HD and PD patients over the past two decades are heterogeneous in design but manifest a common theme: PD provides an early survival advantage that varies in magnitude and duration depending on patients' age, diabetic status, and presence of co-morbidities.

Interestingly, during the same period of time, eight prospective cohort studies have been published on this topic, five of which report no difference in survival outcomes between the two modalities. Specifically with regard to diabetics with ESRD, most studies suggest that younger

Table 1. Potential advantages and disadvantages of in-center hemodialysis and peritoneal dialysis

In-center hemodialysis	Peritoneal dialysis
Advantages	
Effective removal of waste products	Schedule flexibility, easier to travel
Care given by trained professionals	Few risks of dialysis-associated cramps
Regular contact with other patients	Clinic visits limited to 1–2x a month
Rapid correction of electrolyte imbalances	Patient and/or family involved in care
No equipment to store at home	No need for needles or vascular access
Treatment usually occurs only three times a week	Steady state therapy, gentler ultrafiltration
Disadvantages	
Vascular access surgery required	Permanent external catheter; “body-image” problems
Use of large needles	No “off” days
Schedule inflexibility	Risk of peritonitis
Must travel to center three times a week	Risk of weight gain from glucose in dialysate
Cramping with ultrafiltration	Must store dialysis equipment and supplies at home
Risk of bacteremia (with tunneled catheter)	Need for self-monitoring of care

Dialysis modality

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Table 2

Potential benefits of peritoneal dialysis in diabetics who suffer from more severe vascular disease

- Gentler and more gradual ultrafiltration, greater hemodynamic stability
- Vascular surgeries not required for dialysis access
- Better preservation of residual kidney function
- Minimal rapid shifts in electrolytes (potassium, calcium)

diabetics with no additional co-morbidity have a survival advantage while older diabetics with additional co-morbidity have a survival disadvantage when treated with PD. In other subgroups of diabetics, there appears to be no difference in outcomes between patients treated with either of the two dialysis modalities. In these studies, however, the reported statistical differences in hazard ratios translates into small differences in more clinically relevant measures such as life expectancy

of patients treated with HD or PD.

It must also be mentioned that most published studies examining the effect of dialysis modality on survival have drawn their cohorts from patients incident before the year 2000. These older cohorts lacked the benefits of more recent advances in PD such as improvements in connectology, catheter exit-site antibiotic prophylaxis protocols to reduce infection risk, and increased awareness of the importance of solute clearances and careful volume management. All of these PD advances have probably contributed to improvements in PD outcomes, but their benefit has not been well captured in the literature.

A comparison of patient and technique survival in incident HD and PD from 1996 to 2003 has shown that the outcome of incident PD patients progressively improved whereas that of HD patients remained unchanged during the same time period. These improvement trends have continued over the past five years, and a more recent analysis of patients starting dialysis in 2002–04 in the United States shows no significant differences in outcomes between modalities, even among older diabetics treated with either HD or PD.

What can we learn from this varied literature? One must first remember that observational studies, although having

the advantage of large patient numbers and therefore excellent statistical power, depend on information gathered from previously existing patient databases that contain limited details about the clinical condition of individual patients. This limitation makes it difficult to know whether reported differences in these studies are truly an effect of dialysis modality or whether they result from unaccounted differences between the patient groups (HD and PD). Such observational studies are also subject to inaccuracies as a result of nonrandom allocation of patients into two dialysis groups and in most parts of the world, do not necessarily reflect patient choice. Thus, despite the use of advanced statistical analyses, one has to be careful in attributing any differences in outcomes of patients treated with different therapies to the dialysis modality itself.

Given the lack of strong and conclusive data favoring one dialysis modality over another plus the differential changes in outcomes of patients treated with HD and PD over time in the United States, it appears reasonable that neither dialysis modality should be automatically excluded for any diabetic patient with advanced CKD; rather, careful evaluation of medical factors are likely best addressed on an individual level.

The diabetic patient who ultimately

starts HD should take care to limit interdialytic fluid gains and rapid electrolyte shifts, and venous dialysis catheters should be avoided as far as possible. A diabetic starting PD should be prescribed a regimen that minimizes the use of hypertonic glucose-based solutions. Perhaps more importantly, patient preference should play a major role in the decision-making process, but it necessarily requires dialysis education to be provided in a timely and complete manner. Ultimately, the life-saving benefits of dialysis are of no use if the patient is miserable for lack of being given a choice in their dialysis lifestyle. ●

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Goals of Therapy for Patients with Diabetic Nephropathy

By Jamie P Dwyer

Many therapies exist to treat diabetic kidney disease (DKD). Some have been proven to delay the progression of chronic kidney disease (CKD), while others have not been rigorously tested in a controlled way. This article summarizes the major clinical findings that direct DKD treatment and outlines the progress of ongoing trials whose results will direct care.

Glycemic control

Intensive glycemic control reduces albuminuria in type 1 diabetes. The Diabetes Complications and Control Trial (DCCT) randomized 1441 type 1 diabetics (age 13–39) without cardiovascular (CV) disease and with normal kidney function to intensive ($A1c < 6.05$) versus conventional ($A1c \sim 9.0$) glycemic control. Only 73 individuals had microalbuminuria at the start of the study.

Participants were followed for a mean of 6.5 years. Intensive glycemic control reduced the occurrence of microalbuminuria

by 39 percent and overt proteinuria by 54 percent. There were nearly three times as many severe hypoglycemic episodes in the intensive control arm as in the conventional arm. There was no reduction in CV events in the DCCT (probably a result of the cohort's youth), but these same subjects were followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. EDIC showed a 42 percent reduction in any CV event 10 years after both groups had similar glycemic control (implying that the CV effect of intensive glycemic control persisted after control was loosened).

In type 2 diabetes, however, the results are not as clear. An early study (the University Group Diabetes Program [UGDP]) tested the efficacy of tolbutamide, insulin, phenformin, or placebo, and showed no renal, microvascular, or CV benefit, with increased CV death in the tolbutamide arm. The much larger UK Prospective Diabetes Study (UKPDS) tested sulphonylurea or insulin versus dietary control,

and showed no renal benefit, a 25 percent microvascular benefit, and no CV effect, although some subgroups showed a possible effect at 10 years. Three large trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE], and the VA Diabetes Trial [VADT]) (Table 1) have collectively studied nearly 23,000 individuals. CV effects ranged from no benefit to increased risk, and there was variable renal benefit and a significant proportion of hypoglycemia in the intensive groups.

Evidence supports intensive glucose control as renoprotective therapy in type 1 diabetes. The therapy may also benefit patients with type 2 diabetes who are early in the course of disease, who can achieve glycemic control easily, and who are less prone to hypoglycemia. Current evidence does not support extremely aggressive control of hyperglycemia in all

patients with type 2 diabetes.

Single-agent inhibition of the renin-angiotensin system (RAS)

Treatment of type 1 diabetic nephropathy with angiotensin converting enzyme inhibitors (ACE-I) clearly protects against deterioration in renal function. Captopril 25 mg TID was shown to reduce the composite outcome of death, dialysis, or kidney transplantation by 50 percent (relative risk reduction [RRR]; absolute risk reduction [ARR] 9.7 percent, number needed-to-treat [NNT] 10 subjects, for four years). This trial included 409 patients with baseline urinary protein excretion ≥ 500 mg/day and serum creatinine (SCr) ≤ 2.5 mg/dL.

Treatment of patients with type 2 diabetes and early nephropathy (in this case, microalbuminuria) with the angiotensin receptor blocker (ARB) irbesartan has been shown to prevent progression to overt proteinuria. Irbesartan 300 mg daily versus placebo reduced the onset of overt