Dialysis modality
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Dialysis modalities differ in their effectiveness in managing diabetic nephropathy, and these differences in outcomes translate into dialysis modalities. In these studies, patients treated with either of the two groups 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 connectecology, 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 intradialytic 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.

Diabetic Nephropathy

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 directly 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 < 6.0%) versus conventional (A1c = 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 ≤ 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
proteinuria by 0.51 percent (RRR), with ARR 9.7 percent (NNT 10 subjects, for 2 years). Irbesartan 150 mg was not statistically significantly different from placebo in reducing urinary protein excretion.

The treatment of patients with overt proteinuria with irbesartan or losartan has been shown to reduce the composite outcome of doubling of Scr, end stage renal disease, or death, in two large prospective clinical trials (Irbesartan Diabetic Nephropathy Trial [IDNT] and Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [RENAAL] study) (Table 2). Evidence from multiple clinical trials demonstrates that in patients with type 1 or type 2 diabetes and early or late nephropathy, treatment with drugs that inhibit the RAS clearly improves renal outcomes.

Lipid lowering

Multiple small clinical studies have addressed the question of whether improving lipids can delay the progression of kidney disease. No large prospective trials have been done to test this hypothesis adequately. The best available evidence is a meta-analysis that showed that lipid lowering reduced renal outcomes in patients with kidney disease. The effect of these medications, however, may be independent of their lipid-lowering effects.

Blood pressure (BP) control

Despite current guidelines (which urge a BP goal < 130/80 mm Hg for patients with CKD), there are no well-powered, randomized trials that demonstrate in their primary analyses a benefit to this level of BP control. The lack of such trials is due in part to the need for strict BP control, which has the results of the study that form the basis of the guidelines (the Modification of Diet in Renal Disease [MDRD] study) enrolled only 25 subjects with diabetes (essentially excluding them).

No one doubts that an extremely high blood pressure can cause rapid loss of kidney function in DKD. Early studies showed improvement in loss of GFR with lowering BP. In addition, many observational studies or trials in which achieved BP is reported have demonstrated a continuous benefit of lowering BP (e.g., the Heart Outcomes Prevention Evaluation [HOPE] trial), IDNT—although not designed for this specific outcome—showed a decreasing CV risk with achieved systolic blood pressure (SBP) (from > 180 to 120), but those individuals who achieved SBP < 120 had increased CV risk, on par with those who achieved SBP > 180. In other words, more may be less with respect to BP control in DKD.

The cornerstone of the treatment of diabetic nephropathy is delaying the progression of CKD. Control of hyperglycemia and blood pressure, and use of Ras blockade are accepted therapies. Combination therapies and very strict BP control are not, as yet, entirely proven, but ongoing trials will address the limitations of currently completed studies.

Lifestyle modifications

Smoking cessation, weight control, and increased physical activity should be encouraged. It is known that smoking and obesity increase the rate at which kidney disease progresses. For all the other reasons we tell our patients to stop smoking, perhaps “It may keep you from going on dialysis” will be the motivator to get them to quit.

Combination therapies

Multiple small and potentially underpowered studies using surrogate outcomes (e.g., proteinuria) have inconsistent results, but generally support improvement with ACE-I + ARB, or suprapharmacologic doses of ACE-I or ARB in diabetic nephropathy. Only a few trials have addressed the question of what combinations of inhibitors of the RAS are successful at preventing outcomes. The results of the Combination treatment of angiotensin-II receptor blocker and angiotensin-converting enzyme inhibitor in nondiabetic renal disease (COOPERATE) have been called into question and an official retraction has been published; it is therefore excluded from discussion.

The RENAL in the Evaluation Of proteinuria In Diabetes (AVOID) trial studied the effect on proteinuria of adding aliskiren to losartan in type 2 diabetic nephropathy: 599 subjects with type 2 diabetes, hypertension, urinary albumin/creatinine ratio 0.3–3.5 g/g (0.2–3.5 g/g if taking agents that blocked the RAS), and estimated glomerular filtration rate (eGFR) > 30 mL/min/1.73 m² were studied. Aliskiren reduced proteinuria at 24 weeks, but the trial was not long enough to assess the effect of aliskiren on the progression of CKD or CV events. Patients treated with combination therapy developed hyperkalemia (K ≥ 6.0 mEq/L) more often (4.7 percent versus 1.7 percent). The ONgoing Telmisartan Alone in combination with Ramipril Global Endpoint study (ONTARGET) trial studied 25,260 patients with ramipril, telmisartan, or both, for the effect on the composite primary (CV) outcome, namely death from a CV cause, myocardial infarction, stroke, or hospitalization for heart failure. There was no difference in the primary outcome among the three arms. The renal substudy showed less worsening of proteinuria with combination therapy, but GFR decreased more in the combination arm compared to the single-agent arms (by about 2 mL/min/1.73 m²). Additionally, there was a significant increase in the renal endpoint (dialysis, doubling of Scr, or death) in the combination arm compared to single-agent arms. The biggest contributor to this endpoint was the need for acute dialysis (28 cases in combination, 13 and 20 in the single-agent arms).

It may be that the risk-benefit profile for certain combinations of Ras blockade does not apply to all combinations.

| Table 1. Intensive glucose control in type 2 diabetes, showing no compelling benefit |
|---|---|---|---|
| **ACCORD** | **ADVANCE** | **VADT** |
| Population | n = 10,291 with CV event or risk factor | n = 11,140 with CV event or risk factor | n = 1791 with poor BP control |
| Age (x, mean) | 62 | 66 | 60 |
| DM duration (y) | 10 | 8 | 11.5 |
| On insulin at baseline (%) | 35.8% | 1.5% | 7.2% |
| Hemoglobin A1c, baseline | 8.1% | 7.2% | 9.4% |
| ALA target (%) | <6.0% vs. 7.9% | <6.5% vs. routine care (achieved 6.3% vs. 7.0%) | 6.5% vs. 8.4% (1.5% difference) |
| Primary outcome | Increased total and CV mortality in intensive group | No benefit on CV outcomes, reduction in microvascular events | No benefit |
| Renal outcome | No benefit | Albuminuria reduced 21% | No benefit |
| Hypoglycemia (%) | 16.2 | 2.7 | 21.2 |

Many combinations are limited by hyperkalemia, which is more problematic in the “real world” than in a clinical trial.

Future studies

Several ongoing studies may address current uncertainties in the management of diabetic nephropathy. The Department of Veterans Affairs Nephropathy in Diabetes (VA NEPHRON-D) Study is testing whether the combination of the ACE-I losartan and ARB losartan is superior to losartan alone to delay the progression of CKD. Approximately 1900 patients will be recruited until 2013. The Aliskiren Trial In Type 2 Diabetes Using Carc3io-Endpoints (ALTITUDE) Study is testing whether dual RAS blockade with aliskiren and an ACE-I or ARB reduces CV and renal morbidity and mortality. It aims to recruit 8600 patients followed for four years.

Finally, the BP companion study to ACCORD will help elucidate the target BP for diabetic nephropathy caused by type 2 diabetes.

Conclusions

The cornerstone of the treatment of diabetic nephropathy is delaying the progression of CKD. Control of hyperglycemia and blood pressure, and use of RAS blockade are accepted therapies. Combination therapies and very strict BP control are not, as yet, entirely proven, but ongoing trials will address the limitations of currently completed studies.

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