ABSTRACT

Diabetic nephropathy is the single most common cause of end-stage renal disease in the United States. Recently, several major therapeutic interventions have been developed and demonstrated to slow or halt the progression of renal failure in patients with diabetes and diabetic kidney disease. The Diabetes Control and Complications Trial demonstrated that microalbuminuria developed in fewer patients in the intensive blood sugar control group than in the conventional therapy group. Similarly, the risk of developing proteinuria was reduced by intensive blood sugar control. Multiple studies have demonstrated that in patients with insulin-dependent diabetes and proteinuria, lowering the systemic blood pressure slows the rate of decline in renal function and improves patients' survival. In the recently completed trial of ACE inhibition in diabetic nephropathy, ACE inhibitors were specifically shown to decrease dramatically the risk of doubling of serum creatinine or reaching a combined outcome of end-stage renal disease or death. In studies in small numbers of patients with insulin-dependent diabetes and established diabetic nephropathy, dietary protein restriction has also been demonstrated to slow the rate of decline of renal function. New potential interventions currently undergoing study include the use of aldose reductase inhibitors, the use of drugs that prevent the formation of advanced glycosylation end-products, and the use of angiotensin II receptor antagonists. Thus, several established benefits have recently been demonstrated to help prevent the development of or slow the progression of diabetic nephropathy, including blood pressure control, blood sugar control, and treatment with ACE inhibitors. Dietary protein restric-

IMPROVED BLOOD SUGAR CONTROL

Tight control of blood glucose prevents the development of and ameliorates established diabetic nephropathy in animal studies (7,8). Epidemiologic studies have implicated hyperglycemia in the pathogenesis of the long-term complications of diabetes, including renal disease in humans (9–12). Several small studies have demonstrated a beneficial effect of blood sugar control on diabetic kidney disease (13–15). More recently, the Stockholm Diabetes Intervention Study demonstrated a more uniform beneficial effect of intensive blood sugar control in patients with IDDM and established complications (16). However, many of the conventionally treated patients in this study crossed over to the intensive blood sugar-control group. The Diabetes Control and Complications Trial (DCCT) randomly assigned 1,441 patients with IDDM to either intensive therapy consisting of insulin administered with either an insulin pump or by three or more daily insulin injections and guided by frequent blood glucose monitoring coupled with dietary adjustment, or to conventional therapy with one or two daily insulin injections in addition to routine dietary counseling (17). At baseline the patients were in two cohorts: 726 patients with no retinopathy
constituted the primary prevention cohort, and 715 patients with mild retinopathy constituted the secondary intervention cohort. None of the patients had proteinuria at baseline (>40 mg/24 hr) and only 73 of the patients in the secondary cohort had microalbuminuria. The entire cohort of 1,441 patients was followed for a mean of 6.5 yr and 99% of the patients completed the study.

A statistically significant difference in the average glycosylated hemoglobin value was maintained after baseline between the intensive therapy (approximately 7.0%) and conventional therapy (approximately 9.0%) groups in both cohorts. In both cohorts, microalbuminuria (defined as a urinary albumin excretion rate, measured annually, of ≥40 mg/24 hr) developed in fewer patients in the intensive therapy group than in the conventional therapy group, with a risk reduction of 34% in the primary cohort and 43% in the secondary cohort (Figure 1). The risk of developing proteinuria (urinary albumin excretion rate of 300 mg or more per 24 hr) was reduced by 56% in the secondary cohort. Although there was a trend toward preventing subjects from progressing from microalbuminuria to albuminuria in the intensive therapy group compared with the conventional therapy group in the 73 subjects in the secondary cohort with microalbuminuria at baseline, this trend did not reach statistical significance (18). A recent report from Viberti et al. in fewer than 100 patients with IDDM and microalbuminuria found no demonstrable protection from intensive therapy (19). However, the highly statistically significant protection conferred by intensive therapy in the secondary cohort as a whole (715 patients) supports the use of intensive therapy in patients with microalbuminuria. The conflicting results from Viberti et al. and in the 73 patients with microalbuminuria at baseline in the DCCT probably reflect inadequate sample size. Too few patients in the DCCT developed proteinuria and declining renal function to comment on the potential benefit of intensive therapy in this setting. In the DCCT, intensive therapy dramatically reduced the risk of retinopathy and neuropathy. The chief adverse effect associated with intensive therapy was a two-to-threefold increase in severe hypoglycemia. The impact of better blood sugar control may be one of the factors accounting for the reported declining incidence of persistent albuminuria over the last decade, as reported in Scandinavia (20).

ANTIHYPERTENSIVE THERAPY

Multiple studies have demonstrated that in IDDM patients with proteinuria and declining renal function, lowering the systemic blood pressure slows the rate of decline in renal function and improves patient survival (Figure 2) (21-24). Although these individual studies have been done in relatively small numbers of patients, taken cumulatively, the lowering of systemic blood pressure appears to be consistently associated with a slowing of the rate of decline of renal function, despite the fact that in several studies only modest blood pressure control was achieved (Figure 2). The definition of adequate blood pressure control in patients with IDDM is unclear. The Joint National Commission V definition of high normal blood pressure (140/90 mm Hg) may represent frank hypertension in patients with IDDM and diabetic kidney disease. Currently, the Collaborative Study Group is conducting a study in which patients with IDDM and established diabetic kidney disease are randomized to two levels of blood pressure control (mean arterial pressure [MAP])...
<92 mm Hg or MAP ≥100 to 107 mm Hg) to attempt to better define the blood pressure at which kidney function is best preserved (E.J. Lewis, personal communication). Also, in patients with IDDM and microalbuminuria, lowering the systemic blood pressure has been demonstrated to lower albumin excretion rates (25–29). Thus, even in early diabetic kidney disease, the lowering of systemic blood pressure appears to be of benefit.

ACE INHIBITION

Studies in animals with diabetic kidney disease demonstrated that ACE inhibitors preserved renal structure and function independent of their effect on systemic blood pressure (30–32). In these diabetic animals, the mechanism of protection was the removal by ACE inhibitors of the tonic constrictor effect of angiotensin II on the efferent arteriole leading to lower glomerular intracapillary pressures while preserving renal plasma flow. In a meta-regression analysis of 100 studies that provided data on renal function and proteinuria both before and after treatment with an antihypertensive agent in patients with diabetes, only ACE inhibitors were found to decrease proteinuria and preserve glomerular filtration rate independent of changes in systemic blood pressure (33). Treatment with ACE inhibitors in patients with IDDM and microalbuminuria has been reported to decrease the urinary albumin excretion rate and decrease the progression to overt proteinuria (34–36). In an open randomized controlled study of 4 years’ duration, 44 normotensive insulin-dependent diabetic patients with persistent microalbuminuria were randomized to receive either captopril 25 mg or no blood pressure-lowering medication. In the captopril-treated group, the urinary excretion of albumin decreased, whereas there was an increase in urinary albumin excretion in the control group. Seven of the untreated patients progressed to diabetic nephropathy whereas none of the captopril-treated patients developed clinically overt diabetic nephropathy (35). More recently in a randomized double-blind placebo-controlled clinical trial of 2 years’ duration, 92 patients with insulin-dependent diabetes and persistent microalbuminuria but no hypertension were randomly assigned to either captopril 50 mg or placebo twice per day. Twelve patients receiving placebo and 4 receiving captopril progressed to clinical proteinuria (defined as an albumin excretion rate persistently >200 μg and at least a 30% increase from baseline) (36). Albumin excretion rates rose from a geometric mean of 52 to 76 μg/min in the placebo group but fell from 52 to 41 μg/min in the captopril group, a significant difference.

In the recently completed clinical trial of ACE inhibition in diabetic nephropathy, 409 patients with insulin-dependent diabetes were randomized to receive either oral captopril 25 mg three times daily or placebo (37). Patients were included in this trial if they had insulin-dependent diabetes of at least 7 years' duration with onset before age 30, were between the ages of 18 and 49, and had diabetic retinopathy, a urinary protein excretion rate of ≥500 mg/24 hr, and a serum creatinine concentration of ≤2.5 mg/dL. The primary outcome of this trial was time to doubling of serum creatinine concentration to at least 2 mg/dL. Secondary outcomes were time to death, dialysis or transplantation, and the impact of ACE inhibition on urinary protein excretion rate. The blood pressure goals were a diastolic blood pressure below 90 mm Hg and a systolic blood pressure below 140 mm Hg, or if the baseline systolic blood pressure exceeded 150 mm Hg, a subsequent decrease of at least 10 mm Hg and a maximal reading of 160 mm Hg. Blood pressure control was achieved by using a variety of antihypertensives but excluding other ACE inhibitors and calcium channel blockers. Sixty-eight patients had a doubling of serum creatinine concentration-event: 25 in the captopril group and 43 in the placebo group, for a risk reduction of 48% (Figure 3). The beneficial effect of captopril was not altered by any of the baseline covariants except baseline creatinine concentration. A higher baseline serum creatinine value was significantly associated with a decreased risk of a two-fold increase in serum creatinine excretion rate in the captopril group. However, this reflects the fact that there were more doubling of serum creatinine-events for patients who were enrolled with a higher serum creatinine concentration. A patient enrolled with a serum creatinine concentration of 2 mg/dL and a GFR 30 mL/min only had to lose 15 mL/min of GFR to double their serum creatinine concentration. However, a patient who entered the trial with a serum creatinine concentration of 1 mg/dL and a GFR of 70 mL/min had to lose 35 mL/min of GFR before they doubled their serum creatinine concentration. Thus, the statistically significant efficacy of captopril was highly influenced by the outcome chosen, since there were more doubling of serum creatinine-events in patients whose baseline serum creatinine concentration was higher. The sequential measurements of creatinine clearance were analyzed by using a logarithmic transformation that the data best fit. The rate of decline in 24-hour creatinine clearance in the 402 patients with two more determinations was 11% per year in the captopril group and 17% per year in the placebo group (P = 0.03). Expressed in the traditional way of mL/min per year of GFR lost, the placebo group lost at about 6 mL/min per year and the captopril group lost at a correspondingly slower rate. The median urinary protein excretion rate of the patients in the captopril group decreased 0.3 g/day by the first quarterly visit, and remained lower in this group than in the placebo group throughout the remainder of the trial. The aggregate analysis over the 4 yr revealed significantly less proteinuria in the captopril group (P = 0.001).

Sixty-five patients died or reached end-stage renal disease: 23 in the captopril group and 42 in the placebo group, for a risk reduction of 50% (Figure 4).
Figure 3. Cumulative incidence of events in patients with diabetic nephropathy in the captopril and placebo groups. The cumulative percentage of patients who had a doubling of serum creatinine concentration to at least 2.0 mg/dL are shown for the placebo group (squares) and the captopril group (triangles). Adapted from Lewis EJ, Hunsicker LG, Bain RP, Rohde RD for the Collaborative Study Group, The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med, 1993;329:1460. Copyright 1993. Massachusetts Medical Society. All rights reserved.

Figure 4. Cumulative incidence of events in patients with diabetic nephropathy in the captopril and placebo groups. The cumulative percentage of patients who died or required dialysis or renal transplantation are shown for the captopril group (bottom line) and the placebo group (top line). Adapted from Lewis EJ, Hunsicker LG, Bain RP, Rohde RD for the Collaborative Study Group, The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med, 1993;329:1459. Copyright 1993. Massachusetts Medical Society. All rights reserved.
Doubling of serum creatinine concentration was an excellent surrogate for the clinically relevant outcome of time to death, and dialysis or transplantation. Analyzed by the proportional hazards regression model and adjusting for MAP during the follow-up time, the effect of captopril on the preservation of renal function was independent of any effect on systemic blood pressure. The risk reduction associated with captopril treatment was not significantly different in hypertensive or normotensive patients (25% of patients) enrolled in this trial. The administration of captopril also led to decreased proteinuria. There were few adverse events, with only three hyperkalemic events (K+ >6.0 mEq/L) and no reported acute renal failure. This study demonstrated conclusively that captopril was kidney-protective in normotensive and hypertensive patients with insulin-dependent diabetes and clinically evident nephropathy.

**DIETARY PROTEIN RESTRICTION**

In many experimental animal models of renal disease, including diabetes, high dietary protein intake accelerates the deterioration of renal function (38,39). Lower protein diets in animal studies improved glomerular hemodynamics via constriction of the afferent arteriole, proximal to the glomerular capillary tuft. In humans, low-protein diets have been demonstrated to reduce glomerular hyperfiltration, decrease urinary albumin excretion, and slow the rate of decline in renal function (40–43). Unfortunately, all of these studies in humans have had low numbers of patients enrolled. In one study with the largest group of patients (35 patients) observed for the longest duration, the rate of decline in GFR was 1.01 mL/min per month for patients on the 1 g/kg per day protein diet and 0.26 mL/min per month for those on the 0.6 g/kg per day protein diet (Figure 5) (44). In contrast to this beneficial effect of a low-protein diet in studies with relatively small numbers of patients with diabetic kidney disease, the recently completed Modification of Diet in Renal Disease Study (MDRD) in 840 patients with renal diseases other than insulin-dependent diabetes and diabetic kidney disease was unable to demonstrate any benefit to a low-protein diet (45). Whether this conflict in results reflects a different effect of low-protein diets in patients with insulin-dependent diabetes and diabetic kidney disease and other kinds of kidney disease or is the result of the dramatic difference in sample size (35 versus 840 patients) is uncertain.

Interestingly, the Recommended Dietary Allowance of protein is 0.8 g/kg per day. This is substantially lower than the protein content of the average American diet, which often exceeds 1.5 g/kg per day. Currently available data in patients with IDDM and diabetic nephropathy support a beneficial effect of lowering dietary protein intake.

**ALDOSE REDUCTASE INHIBITORS**

Many of the tissues demonstrating the most severe complications of diabetes, including the kidneys, eyes, retina, and peripheral nerves, do not require insulin for the uptake of glucose and possess the enzyme aldose reductase (46). Substantial evidence suggests that excess glucose in these tissues is metabolized via the polyol pathway. It has been postulated that the
resulting accumulation of sorbitol and decrease in myo-inositol levels in these tissues are responsible for the end-organ complications of diabetes. Aldose reductase and sorbitol dehydrogenase comprise the polyol pathway (47). Drugs that inhibit aldose reductase have been demonstrated to diminish the onset of proteinuria in streptozocin-induced diabetic rats (48). In humans with diabetes, aldose reductase inhibition in preliminary studies decreased urinary albumin excretion rates (49). Aldose reductase inhibitors have also been demonstrated preliminarily to improve nerve conduction and retinopathy in patients with IDDM (50).

**PREVENTION OF THE FORMATION OF ADVANCED GLYCOSYLATION END-PRODUCTS**

It has been hypothesized that advanced glycosylation end-products (AGE) accumulate in tissues in diabetics and may, at least in part, be responsible for the end-organ complications of diabetes (51). Glucose forms chemically reversible early-glycosylation products with proteins at a rate proportional to the glucose concentration. Some of these early glycosylation end-products on long-lived proteins undergo a complex series of chemical rearrangements, forming irreversible glycosylation end-products that are capable of forming covalent crosslinks. These events do not reverse when hyperglycemia is corrected. Macrophages have receptors for these advanced glycosylation end-products and this interaction stimulates monokine production (51). Glycation of albumin may contribute to its loss across the glomerular basement membrane, and the accumulation of glycosylated protein in the glomerulus may stimulate mesangial expansion (52–54). AGE accumulate faster than normal in patients with diabetes and their accumulation parallels the severity of renal functional impairment in diabetic nephropathy (55). Aminoguanidine, a nucleophile hydrazine compound, prevents the formation of advanced glycosylation end-products and the formation of glucose-derived collagen crosslinks in vivo and in vitro (56). When given to diabetic rats, this drug has been found to decrease albuminuria and glomerulosclerosis. In one study, aminoguanidine was found to decrease glomerular basement membrane thickening but not mesangial expansion, whereas the opposite was found in another study (54, 55). A clinical trial using aminoguanidine in patients with IDDM and established nephropathy is ongoing.

**SUMMARY**

Diabetic nephropathy is a devastating complication for patients with IDDM. Several established benefits, including blood pressure control, blood sugar control, and treatment with ACE inhibitors, can help prevent the development or slow the progression of this complication. Dietary protein restriction may also be of benefit. Treatment with aldose reductase inhibitors or inhibitors of the formation of advanced glycosylation end-products are currently undergoing experimental interventions.

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