Preventing or slowing the progression of diabetic nephropathy

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Presented at Internal Medicine Grand Rounds, BUMC, July 21, 1998

Diabetes is the most important cause of end-stage renal disease (ESRD) in the USA. According to recent data, 40% of all new patients entering ESRD programs are diabetics (1), leading to a cost of >$4 billion annually (2). The exact percentage of patients with type I and type II diabetes who will progress to ESRD has been debated (3). For type I patients, up to 30% will develop nephropathy and most will progress to ESRD, whereas a smaller percentage of type II patients will progress to ESRD (3). Nevertheless, because type II diabetics make up a far greater percentage of the overall diabetic population, the total number of diabetics who progress to ESRD is weighed towards type II rather than type I patients. In addition, white patients have a lower risk of developing ESRD than do blacks, Hispanics, or American Indians with type II diabetes (3).

Over the past several years, a number of important studies have proved that the course of diabetic nephropathy and other diabetic complications may be altered by appropriate interventions (4, 5). How great the total sum of ideal intervention will be and whether these interventions can be applied to the overall diabetic population remains to be seen.

CLINICAL MANIFESTATIONS AND COURSE OF DIABETIC NEPHROPATHY

At the earliest stage of diabetic glomerulopathy, before there is any elevation of the blood urea nitrogen, creatinine, or clinical proteinuria on routine dipstick, most patients who are destined to progress to clinical nephropathy have an increase in glomerular filtration rate. This is associated with an increase in renal blood flow and an increase in renal size when kidneys are measured ultrasonographically. In the animal model, this hyperfiltration and increase in renal blood flow correlate with an increase in transcapillary glomerular pressures, i.e., intraglomerular hypertension. In this model, an increase in intraglomerular transcapillary pressure is associated with the development of proteinuria and glomerulosclerosis (6, 7). Mechanisms that decrease the intraglomerular transcapillary pressures (e.g., low-protein diet and use of angiotensin-converting enzyme [ACE] inhibitors and angiotensin II [AII] receptor antagonists) are associated with a decrease in both proteinuria and glomerulosclerosis.

At the earliest phase of diabetic renal disease, abnormal levels of albumin will be present in the urine. Routine dipstick and standard laboratory assays for albumin will not detect albuminuria at this level, i.e., microalbuminuria. Testing for microalbuminuria may be done on a 24-hour urinary specimen (>30 mg/24 hr), on a timed specimen (>20 μg/min), or on a spot urine (>30 mg/g creatinine). Several factors can interfere with the detection of microalbuminuria and lead to a high urinary level that does not necessarily imply incipient diabetic nephropathy. These include uncontrolled hyperglycemia, exercise, urinary infections, severe systemic hypertension, congestive heart failure, and acute febrile illness. In the diabetic patient without clinically detectable, dipstick-positive proteinuria, screening for microalbuminuria should be performed.
annually in type I diabetics after 5 years of diabetes or at puberty, and in all type II diabetics. At
least 2 of 3 collections done in a 3- to 6-month period should show elevated levels to establish
the presence of microalbuminuria.

In the majority of type I diabetics, microalbuminuria predicts the progression to clinical
proteinuria. Almost 80% will progress to overt nephropathy in a 10- to 15-year period. Given
the presence of clinical proteinuria (>300 mg/day), most patients with type I diabetics will
progress to ESRD, but at a variable rate (with a loss of glomerular filtration rate [GFR] from 2
to 20 cc/min/year). By 10 years of clinical proteinuria, 50% of type I diabetics will have
developed ESRD; by 20 years, the number will have risen to >75%. The percentage of type II
diabetics initially found to have microalbuminuria will be greater than the percentage of type I
diabetics with microalbuminuria, but only about 20% of type II diabetics will progress to ESRD
within 20 years of developing clinically overt proteinuria. In some studies of type II diabetics,
microalbuminuria has been a predictor not only of clinical nephropathy, but also of
cardiorenal disease (8, 9). In several studies, the rate of decline of renal function has been
the same between type I and type II diabetics, once there is a reduced GFR with clinical
nephropathy (8). If one examines the renal biopsies of diabetics, it is virtually impossible to
distinguish the biopsy of a patient with type I diabetes from that of a patient with type II
diabetes. Both patients with significant glomerulopathy may have nodules of intercapillary
glomerulosclerosis (Kimmelstiel-Wilson nodules), mesangial sclerosis, arteriolar sclerosis of
the afferent and efferent arterioles, and thickening of the glomerular capillary walls. The only
feature on these biopsies that correlates with duration of diabetes and degree of clinical
proteinuria is the thickening of the glomerular basement membranes. All the capillary basement
membranes in the body of a diabetic become thickened over time, but the glomerular ones,
perhaps through their filtration process, are the thickest.

As the GFR declines, proteinuria increases to larger, clinically evident amounts and eventually
reaches >3 to 3.5 g/day. At this point of nephrotic range proteinuria, many patients develop
other manifestations of the nephrotic syndrome, with hypoalbuminemia, edema,
hyperlipidemia, and a coagulation tendency. Most of the patients will develop systemic
hypertension. Diabetes is, by far, the most common cause of the enigmatic syndrome in the
USA. It is extremely unusual for a diabetic patient to progress to ESRD without becoming
hypertensive along the way. Moreover, retinopathy detectable on ophthalmologic examination
is almost always present in type I diabetics with clinical renal disease, and it is often present in
type II diabetics (10).

PREVENTION AND AMELIORATION OF NEPHROPATHY—ESTABLISHED
FACTORS

Hyperl glycemic control

Within the past few years, several studies clearly have shown that good glycemic control is
associated with reduced complications of diabetes in certain populations. The Diabetes Control
and Compliance Trial followed 1400 type I diabetics for >7 years (4). The group randomized to
“tight” control was administered either 3 or more insulin injections a day or given an insulin
pump. There was significantly better control of capillary glucose measurements at several
points during daily measurement (e.g., breakfast, lunch) and better control of the HgbA1c
levels. In the group without retinopathy, presumably with less fixed damage already, there was
a significant reduction in microalbuminuria but not in clinical proteinuria. In the group with
retinopathy, “tight” glucose control led to less microalbuminuria and to significantly less clinical proteinuria. There was also a reduction in retinopathy and neuropathy in the well-controlled group. A recent study in Japanese type II diabetics has shown similar results (11). Thus, although there is somewhat less data for the type II patient, good glycemic control should be a part of every diabetic’s care. This may be a major factor in preventing nephropathy and in slowing its rate of progression. The exact method of control is left for the clinician to decide.

**Systemic hypertension control**

Many recent studies have focused on the medication of choice to control hypertension in patients with diabetes (12). It is important to realize that control of hypertension, regardless of the method, is crucial in slowing the progression of nephropathy. In type I diabetics, hypertension develops along with microalbuminuria, and more than one third of type II diabetics have hypertension at the time of their diagnosis with diabetes. In both groups of patients, there is generally an increase in plasma volume and low plasma renin activity. However, the renin-angiotensin-aldosterone axis may be too stimulated for the degree of volume in these patients. Certainly, that would allow for the effectiveness of medications suppressing the system, such as ACE inhibitors and AII receptor antagonists. Both systolic and diastolic hypertension have been correlated with the progression of diabetic nephropathy.

In classic studies done by Parving and colleagues (13, 14), control of blood pressure was shown to decrease GFR decline and proteinuria over years. Because these studies were conducted before the advent of ACE inhibitors, calcium channel blockers, or AII receptor antagonists, the effect of blood pressure control itself clearly makes a clinical difference and leads to a reduction in mortality rate and in the need for dialysis or transplantation.

The ideal blood pressure for the diabetic patient has been the concern of many investigators and clinicians (15). Some guidelines recommend a blood pressure of <130/85 mm Hg for nonpregnant diabetics who are >18 years of age. The recommendations are more modest for isolated systolic hypertension and hypertension in older individuals. Other measures to reduce blood pressure and cardiovascular risk, such as reducing weight, limiting sodium intake, limiting alcohol use, and exercising, should also be instituted. Despite evidence for the beneficial effect of individual types of medications, the overwhelming importance of just controlling hypertension in diabetics cannot be overemphasized!

**ACE inhibitors and AII receptor antagonists**

Angiotensin II has been shown in animal models to have several detrimental effects upon the glomerulus (7). It may increase efferent arteriolar vasoconstriction, leading to associated intraglomerular hypertension, proteinuria, and glomerulosclerosis. It may also promote mesangial proliferation and sclerosis and act as a growth factor on various glomerular cells. These effects have been ameliorated or reversed in cell culture and in animal studies (16) by the use of either ACE inhibitors or AII receptor antagonists (7). In cell culture, AII receptor antagonists prevent mesangial cell proliferation and the production of matrix proteins (16). In humans, studies clearly show benefits from the use of ACE inhibitors in the diabetic population (17, 18).

In a classic study of type I diabetics, over 400 patients were randomized to receive the ACE inhibitor captopril or a placebo 3 times a day with other medications to control blood pressure
Over 4 years of follow-up, the patients in the captopril group had a significantly lower percentage of creatinine increase, in addition to a 50% reduction in the death rate, the need for dialysis, and the need for transplantation when compared with the placebo group. This effect was present despite the fact that blood pressure control was similar in both groups (140/90 mm Hg). This study showed the benefits of ACE inhibitors in type I diabetics. It did not, however, include any type II diabetics, use calcium channel blockers in the control group, or imply this was a specific effect of a single ACE inhibitor, captopril. (A follow-up study in this population was being performed with a different ACE inhibitor.)

A long-term trial examining 100 normotensive type II diabetics having microalbuminuria found that the group randomized to enalapril showed no progression to clinical proteinuria over 7 years of follow-up (19). In the control group, there was progression to clinical proteinuria. These and other studies on microalbuminuric hypertensive patients suggest that ACE inhibitors have, by their unique intrarenal effects, advantages over other classes of medications in preventing the progression to renal failure in diabetics. Recently in Europe, a large trial with benazepril found a reduction in proteinuria and renal deterioration in patients with glomerular diseases (18). Although there were few diabetics in this study and almost no blacks, the role of ACE inhibition in glomerular diseases has been established.

Angiotensin II receptor antagonists are now available, and many new drugs in this class are reaching local pharmacies. These drugs have an advantage because they do not block kininase as all ACE inhibitors do; they will not cause coughing and rarely will cause angioedema, significant side effects of ACE inhibitors. In several trials, they also seem to be associated with less hyperkalemia, but the incidence of increased serum creatinine in patients with marginal renal blood flow is equal to that of ACE inhibitors. In humans, over the short term, these drugs decrease 24-hour proteinuria as well as the ACE inhibitors (e.g., 50 mg and 100 mg of losartan were as effective as 10 mg and 20 mg of enalapril) (20). In diabetic animals, these drugs reduce proteinuria and prevent glomerulosclerosis (7), but they have not yet been shown to slow the progression of diabetic glomerulopathy in humans. Several large studies currently are being conducted with AII receptor antagonists in populations of type II diabetics with early nephropathy.

Although many groups presently recommend ACE inhibitors as the treatment of choice for diabetic patients with hypertension or microalbuminuria, recent data suggest that some calcium channel blocking medications also can slow the progression of diabetic nephropathy (21). These studies have shown both reduction of proteinuria and slowing of the decline in GFR over time. The best data come from comparative studies using nondihydropyridine calcium channel blockers. In some trials, these drugs appeared to be as effective as ACE inhibitors in preventing the progression of diabetic nephropathy. These studies have been performed in a small number of patients, and it is unclear whether these data can be extrapolated to other diabetic populations or to other newer medications of the same class of agents.

Recent large, blinded, randomized trials using AII receptor antagonists have used calcium channel blockers in the control arms; however, the calcium blocker control group of the Appropriate Blood Pressure Control in Diabetes trial in type II diabetics was terminated recently because of an increased mortality from cardiovascular disease (21). Further ongoing studies should clarify the picture in the future and show which calcium channel blockers are effective and safe in the diabetic population.
Dietary protein restriction

In diabetic animals, dietary protein restriction leads to a reduction in intraglomerular capillary hypertension and to less proteinuria and glomerulosclerosis (Rennke MG, Sandstrom B, Zatz R, Meyer TW, Cowan RS, Brenner BM: The role of dietary protein in the development of glomerular structural alterations in long-term experimental diabetes mellitus. American Society of Nephrology. New Orleans, La., USA, December 15?18, 1985. Kidney Int 1986;29:289 [abstract]). In the diabetic human, protein restriction leads to a reduced progression of renal disease (22, 23). In the largest trial of dietary protein restriction, the Modified Diet in Renal Disease Study (23), dietary protein restriction led to equivocal results in renal protection. It should be noted that only 3% of the study’s patients had type II diabetes.

Protein restriction may be particularly difficult in diabetic patients, many of whom are already calorie, saturated fat, cholesterol, sodium, and potassium restricted! Nutritional deficiency with protein restriction has not been studied over the long term in this population. Some recommend a dietary protein restriction to 0.8 g/kg/day in diabetics and a further restriction to 0.6 g/kg/day in those patients with a reduced GFR. Many, including myself, would not recommend dietary protein restriction at this time for the following reasons: 1) it is the least proven method of delaying the progression of nephropathy, 2) its long-term consequences need to be studied, and 3) it is unclear if inhibitors of the rennin-angiotensin system do the same thing in these patients as they do in animal models.

PREVENTION OF DIABETIC NEPHROPATHY IN THE FUTURE

Several new methods of preventing or ameliorating diabetic nephropathy are being studied. There are interesting animal data on the use of aldose reductase inhibitors, but human trials so far have not given promising results. Vitamin E as an antioxidant is being studied in diabetics with early nephropathy and microalbuminuria. Vitamin E has been shown to decrease many markers of oxidative stress but has not yet been clearly shown to decrease microalbuminuria. In the diabetic animal model, advanced glycation end products (AGEs) are associated with retinopathy and nephropathy; aminoguanidine, an experimental medication, prevents AGE formation and cross-linking, causing less retinopathy and nephropathy (24).

A 4-year, randomized, blinded trial in type I diabetes is just being completed. Demonstrating any benefit from newer medications will be more difficult because all patients will now have close monitoring of their blood pressure and blood glucose. Nevertheless, the promise for the future in slowing the progression of diabetic nephropathy, and perhaps in preventing it, is exciting.

References


