Preserving the Diabetic Kidney

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End stage renal disease is an increasingly common problem among both type 2 and type 1 diabetic patients. It is possible to halt or delay the progression from microalbuminuria to proteinuria to end stage renal disease through early screening and aggressive control of blood pressure, blood glucose, and the appropriate use of angiotensin-converting enzyme inhibitors.

KEY WORDS. Diabetic nephropathies; angiotensin-converting enzyme inhibitors; end stage renal disease; albuminuria. *(J Fam Pract 1998; 46:21-28)*

Diabetes is the most common cause of end stage renal disease (ESRD) in the United States, and the disease burden is divided with 60% in patients with type 2 diabetes and 40% in patients with type 1 diabetes. Although nephropathy is a more frequent complication in patients with type 1 than type 2 diabetes, there are many more patients with type 2 diabetes in the general population.[1,2] Worldwide, an estimated 100,000 patients with diabetes are receiving renal replacement therapy.[2] In some populations virtually all patients with diabetes have type 2 diabetes, and these patients constitute 75% to 80% of all new cases of ESRD.[3] African Americans, Latinos, and Native Americans suffer disproportionately high rates of ESRD, approximately 3 to 8 times higher than the rates reported in the white population.[1] The prognosis for patients with type 2 diabetes needing renal replacement therapy in the United States is poor because the mortality rate is 50% greater for patients with diabetes and ESRD than for those with ESRD attributable to other causes.[1,3,4] The only way for healthcare providers to make an impact on these sobering statistics is to support diabetes prevention activities and to intervene at the earliest stage of diabetic kidney disease.

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STAGES OF DIABETIC NEPHROPATHY

Stage I is the onset of diabetic kidney disease, wherein renal function changes consist of increased glomerular filtration and kidney hypertrophy. These changes are not clinically evident, and are reversible with good glycemic control. *Stage II* is also reversible and is characterized by normal albumin excretion. (Definitions for key terms used in diabetic nephropathy are in Table 1.) Renal lesions are found on biopsy in this stage.[5] In *stage III* microalbuminuria is the first clinically detectable sign of diabetic nephropathy, and is thought to be reversible as well.[4,6] The average increase in albuminuria in patients with type 1 diabetes without intervention is approximately 20% per year.[7] Many patients present with microalbuminuria or proteinuria at diagnosis with type 2 diabetes since this form of diabetes may remain undiagnosed for several years. Blood pressure usually starts to increase once fixed microalbuminuria exists. *Stage IV* is overt nephropathy (albumin/protein excretion of >300 mg per 24 hours of protein); the stage when a dipstick will be positive for urinary protein. Kidney damage at this stage is considered to be irreversible and renal function starts to decline at a gradual rate of 1 mL per minute per month.[8] Without any treatment at this stage, uremia and death occur in 7 to 10 years. Because of delayed diagnosis, up to 15% of patients present with stage IV diabetic nephropathy when they receive a diagnosis of type 2 diabetes.[9] *Stage V* is end-stage renal disease that is characterized by elevated blood urea nitrogen and creatinine levels, hyperkalemia, and fluid overload.

TABLE 1

Definitions of Key Terms Used in the Five Stages of Diabetic Nephropathy

Normal albumin excretion: Albumin excretion of < 30mg per 24 hours or <30mg/g creatinine.

Microalbuminuria: Albumin excretion of 30 to 300mg per 24 hours or 30 to 300mg/g creatinine. Note that these patients will have a negative urine dipstick for protein.

Macroalbuminuria/Proteinuria/Nephropathy: Albumin/protein excretion >300mg per 24 hours or >300mg/g creatinine. Even a trace positive urine dipstick is indicative of proteinuria in the absence of contamination or urinary tract infection.

Chronic Renal Insufficiency (CRI)*: Serum creatinine >1.5 mg/dL or creatinine clearance <80% of predicted.

*CRI is defined as a creatinine >1.5mg/dL or creatinine clearance <80% of predicted. Use the following formula to calculate creatinine clearance:

$$\text{Males: CrCl (mL/min)} = \frac{(140\text{-age})(\text{LBW}^{\dagger})}{72\ (\text{Serum creatinine})}$$

Females: Use the above equation and multiply by 0.85

†Lean body weight (LBW) = Males: 50 kg/5 ft + 2.3 kg/inch
Females: 45 kg/5 ft + 2.3 kg/inch

MICROALBUMINURIA

The prevalence of microalbuminuria in patients with type 2 diabetes is 19% to 37%.[10] However, among a population of Pima Indians, microalbuminaria was detected in 8% of those with normal glucose, 15% of those with impaired glucose tolerance, and 47% of those with diabetes. Thus the higher than normal levels of blood glucose that precede the development of diabetes may contribute to the development of microalbuminuria.[11]

What Causes Microalbuminuria?

Much of what we know about the epidemiology of microalbuminuria we have learned from studying the Pima Indians. Since other ethnic groups have not been studied as extensively as the Pima, it is not clear if the epidemiology of diabetic kidney disease is the same in other ethnic groups. Prospective studies have shown that poor metabolic control, hypertension, longer duration of diabetes, and cigarette smoking are all risk factors for the development of microalbuminuria.[3,11-14] Conversely, intensive glycemic control in patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) reduced the occurrence of microalbuminuria by 39%.[15] There is also some interesting data from Pima Indians that pre-diabetic blood pressure predicts the presence of microalbuminuria after the onset of type 2 diabetes.[16] Pre-diabetic albumin excretion was also found to be an independent predictor of albumin excretion after the development of type 2 diabetes among Pima Indians. It is speculated that the level of albumin excretion in patients with diabetes may indicate renal susceptibility that only becomes manifest in the presence of diabetes.[17] There may also be an inherited susceptibility to renal disease: Among the Pima Indians, proteinuria occurred among 14% of diabetic offspring if neither parent had proteinuria, 23% if one parent had proteinuria, and 46% if both parents had proteinuria.[18,19]

Prognostic Value of Microalbuminuria

Microalbuminuria indicates an increased risk for progression to overt nephropathy. Patients with microalbuminuria are between 9 and 20 times more likely to progress to nephropathy than patients without microalbuminuria.[3,4,20] All-cause mortality increases 148% with the presence of microalbuminuria, and cardiovascular mortality increases up to 15-fold.[2, 9, 12, 21, 22] The presence of microalbuminuria can also predict the development of complications such as retinopathy: In one 11-year follow-up study, nearly 70% of patients with diabetes with microalbuminuria developed retinopathy as opposed to zero in the group without microalbuminuria.[23]

Screening

The National Kidney Foundation[3] recommends annual screening for the presence of microalbuminuria for all those who are dipstick negative for proteinuria. Recent heavy exercise, nonsteroidal anti-inflammatory drug use, and urinary tract infections may give a false-positive test for albuminuria. A Micral (Boehringer Manheim Corporation, Indianapolis, Ind) dipstick is one example of an easy and sensitive screening test to detect microalbuminuria (94% sensitivity and 87% specificity compared with ELISA-test package insert). Ward et al[24] found the Micral test to be reliable when compared with 24-

FIGURE 1

Cumulative percentage of patients who developed microalbuminuria among conventional or intensively treated patients with type 2 diabetes. (*P* = .04) Adapted from Ohkubo et al,[25] with permission.

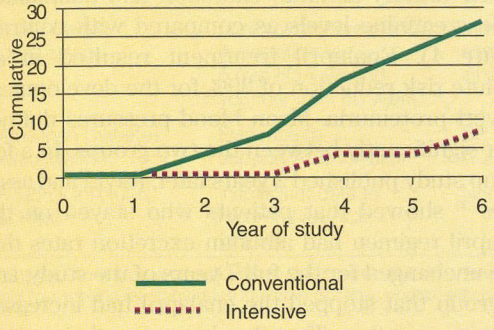
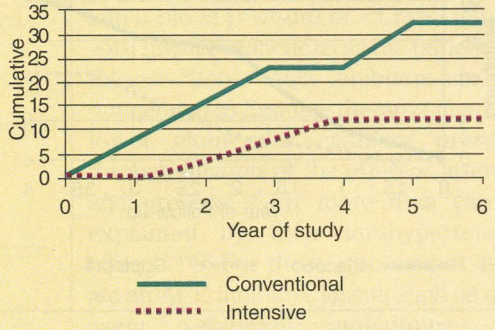


FIGURE 2

Cumulative percentage of patients who progressed from microalbuminuria to albuminuria among conventional or intensively treated patients with type 2 diabetes. (*P* = .05) Adapted from Ohkubo et al,[25] with permission.



hour urine tests for albumin. Since the Micral test is a screening test, a 24-hour urine test or an albumin/creatinine ratio should be performed for confirmation.

INTERVENTION TRIALS

Glycemic Control

The Kumamoto study[25] randomized 110 patients with type 2 diabetes to intensive or conventional insulin treatment for 6 years. They found that intensive glycemic control prevented the onset of microalbuminuria compared with conventional treatment, and that for those with microalbuminuria, it prevented the progression to proteinuria. The glycemic threshold to achieve this prevention benefit was a glycosylated hemoglobin (Hb A_{1c}) of <6.5%. When compared with the patients with type 1 diabetes studied in DCCT,[15] the risk reduction in this group of type 2 patients was even more striking: 70% compared with 39% to 54% in the DCCT (Figures 1 and 2).

Blood Pressure Control

The Modification of Diet in Renal Disease (MDRD) study showed that patients with renal disease had a slower progression of their renal disease if they were kept at a mean arterial blood pressure (MAP) of <92 mm Hg.[26] (Mean arterial blood pressure equals one-third systolic blood pressure plus two-thirds diastolic blood pressure.) This level of blood pressure control may be more important for those with >1 g per day of proteinuria than for those with less significant proteinuria. In untreated hypertensive patients with diabetic nephropathy, glomerular filtration rate (GFR) declines approximately 1/mL per minute per month; antihypertensive treatment can slow this rate of decline by about two thirds.[27]

Treatment with Dietary Protein Reduction

Several studies have indicated that dietary protein restriction decreases proteinuria and slows the decline in GFR in patients with type 1 diabetes compared with controls.[28] However, the MDRD study, a controlled trial designed to look at this question, showed no benefit from protein restriction, though only 3% of the patients had ESRD secondary to diabetic nephropathy and 44% were being treated with an angiotensin-converting enzyme inhibitor (ACE inhibitor), which may have obscured the dietary effect. In addition, most of the patients were consuming less than 1 g per kilogram of body weight per day of protein, which is significantly less than most Americans consume.[26] It would presumably be beneficial to lower the 2 g/kg of body weight per day that many Americans consume to <1 g/kg of body weight per day, and the American Diabetes Association recommends reductions to 0.8 g/kg of body weight per day or ~10% of calories in those with proteinuria.[29] Other studies have determined that animal protein is

FIGURE 3

Percentage of patients with type 1 diabetes who died or needed dialysis or transplantation in placebo or captopril groups. (*P* = <.005 for 4th and 5th years) Adapted from Lewis et al,[30] with permission.

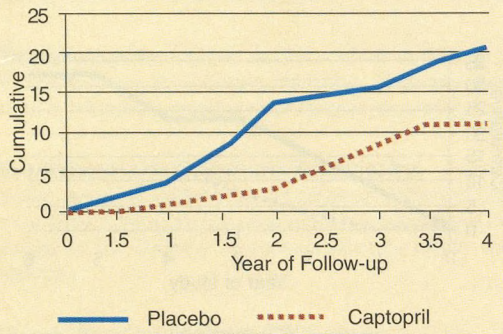
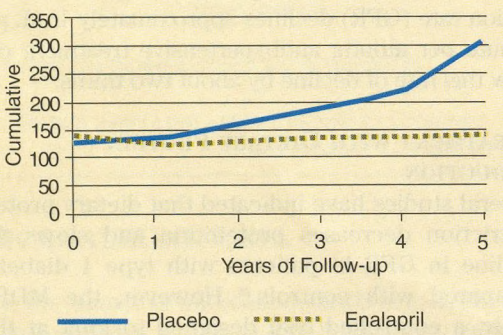


FIGURE 4

Proteinuria in mg/24 hour during 5-year follow-up in patients with type 2 diabetes treated with placebo or enalapril. Adapted from Ravid et al,[31] with permission.



more detrimental than vegetable protein.[2]

ACE Inhibitor Trials

Lewis et al[30] randomized 409 patients with type 1 diabetes with diabetic nephropathy and creatinine <2.5 mg/dL to captopril or placebo-treated groups. They found that the risk of doubling of serum creatinine over 3 years and the combined risk of death, dialysis, and transplantation was reduced by 50% in the captopril group. The authors concluded that captopril protects against deterioration in renal function in these patients with nephropathy by a mechanism independent of the drug's antihypertensive properties, since blood pressures were not significantly different between the two groups. (Figure 3)

Ravid et al[31] randomized 94 normotensive type 2 diabetic patients with microalbuminuria and normal renal function to enalapril (10 mg/day) or placebo in a double-blind format and followed them for 5 years. The enalapril-treated patients showed stabilization of their urinary albumin excretion and maintained stable creatinine levels as compared with controls (Figure 4). Enalapril treatment resulted in an absolute risk reduction of 30% for the development of overt proteinuria. Mean blood pressures did not differ significantly between the two groups. In a follow-up study published 2 years later, Ravid and associates [32] showed that patients who stayed on the enalapril regimen had albumin excretion rates that were unchanged for the full 7 years of the study, and the group that stopped the enalapril had increased albumin excretion. The placebo group that started enalapril for the last 2 years of the study fared better than the group that never received enalapril. This seems to indicate that the earlier the ACE inhibitor is started, the better, and it is never too late to get beneficial effects from an ACE inhibitor.

Other researchers have found similar results with both normotensive and controlled hypertensive patients with type 1 and type 2 diabetes who have been treated with captopril or enalapril. Albumin excretion rates fell in treated patients, and there was less progression to proteinuria when compared with controls.[6,33-36] A more recent study shows that ACE inhibitors provide protection against progression of renal insufficiency in patients with a variety of renal diseases, not just diabetic nephropathy.[37]

TREATMENT OF MICROALBUMINURIA IN DIABETIC PATIENTS

Patients with Type 1 Diabetes

There is general consensus that normotensive patients with type 1 diabetes and persistent microalbuminuria should be treated with an ACE inhibitor regardless of their blood pressure.[3,4,9,36,38]

Patients with Type 2 Diabetes

The recommendations for type 2 patients with diabetes, normal blood pressure, and persistent microalbuminuria are not as sharply defined. The National Kidney Foundation (NKF) convened an expert panel that reviewed 425 publications to

TABLE 2

Treatment Recommendations for Patients with Type 2 Diabetes*

Groups Offering Recommendations†	Microalbuminuria without Hypertension	Microalbuminuria with Hypertension
National Kidney Foundation	ACE inhibitor	BP goal <130/85 mm Hg; ACE inhibitor appropriate
World Health Organization	Antihypertensive therapy if diastolic rises by 5 mm Hg/year and younger than 60 years	Meticulous BP control, especially with ACE inhibitor
American Diabetes Association	Evidence to support ACE inhibitor	BP control, especially ACE inhibitor
National Institutes of Health	Insufficient data to recommend ACE inhibitor	Not discussed

*Adapted from Mogensen CE, Keane WF, Bennett PH, et al,[38] with permission.
†All four groups recommended intensive glycemic control with Hb A_{1c} <7.5 to 8.0.

TREATMENT OF HYPERTENSION

All groups agree on the need for careful control of blood pressure in hypertensive microalbuminuric diabetic patients. The goal for patients with diabetes is to maintain a blood pressure of <130/85 mm Hg with further reductions as the patient can tolerate them.[43] ACE inhibitors are recommended as first-line therapy since they lower glomerular capillary pressure through dilation of the efferent arteriole and preserve GFR more than can be explained by their antihypertensive effects.[8,9,44,45] For those who cannot tolerate an ACE inhibitor, agents such as diltiazem, verapamil, amlodipine, and

establish practice guidelines for patients with type 2 diabetes and microalbuminuria.[3] Their treatment strategy can be seen in Figure 5. Glycemic control should be the first goal, with ACE inhibitor added after glycemic control is achieved. Blood pressure should be maintained at less than 130/85 mm Hg (Figure 5).

Other groups from the World Health Organization (WHO), American Diabetes Association (ADA), and National Institutes of Health (NIH) have come out with recommendations that differ only slightly[38] (Table 2).

After their literature review, Mogensen et al[38] concluded that "early ACE inhibition may slow the progression of renal disease in such patients with microalbuminuria, even when BP is 'normal'." Blood pressure in excess of 130/85 mm Hg should be considered abnormal, and evidence points to benefits in reductions of blood pressure to a lower level (<120/80 mm Hg or mean arterial pressure of 92).[29]

A treatment strategy for the treatment of different stages of diabetic kidney disease can be seen in Table 3. Glycemic control is important until the stage of chronic renal insufficiency, and then it becomes more important to keep the blood pressure at <120/75. There is evidence to support the use of an ACE inhibitor at all stages, including microalbuminuria without hypertension, though this is the area in which the consensus guidelines of the four groups (NKF, ADA, NIH, and WHO) differ.

FIGURE 5

Management guidelines for persistent microalbuminuria. Adapted from Bennett et al,[3] with permission.

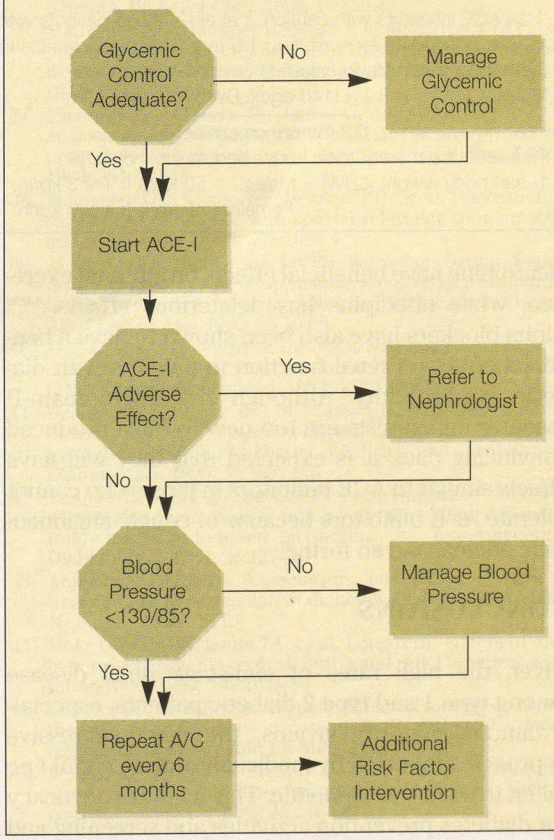


TABLE 3

Treatment Strategies for Patients with Type 2 Diabetes

	Without Hypertension	With Hypertension
Microalbuminaria	Glycemic control Consider ACE inhibitors Close BP monitoring	Glycemic control BP goal <130/85 mm Hg ACE inhibitors
Proteinuria	Glycemic control ACE inhibitors Protein ~10% of total calories Close BP monitoring	Glycemic control ACE inhibitors Protein ~10% of total calories BP goal <130/85 mm Hg
Chronic Renal Insuffiency (CRI) †	ACE inhibitors* Protein ~ 10%of total calories	ACE inhibitors* BP goal <125/75[39] Protein ~10% of total calories <2 g sodium per day Loop diuretic helpful[40]

Note: NSAIDs and cigarettes should be avoided in all patients. Elevated lipids should be treated aggressively, and all patients should be encouraged to participate in a regular program of low-impact exercise because of its beneficial cardiovascular effects. Tight glucose control has been shown to slow disease progression at all stages up to and including proteinuria.[19,41,42] Pregnancy and preexisting hyperkalemia are contraindications to the use of ACE inhibitors.

*Use ACE inhibitors with caution, if at all, in those patients with creatinine >3 mg/dL

†CRI is defined as a creatinine >1.5 mg/dL or creatinine clearance <80% of predicted. Use the following formula to calculate creatinine clearance:

$$\text{Males: CrCl (mL/min)} = \frac{(140\text{-age})(\text{LBW}^{\ddagger})}{72\ (\text{Serum creatinine})}$$

Females: Use the equation above and multiply by 0.85.

‡Lean body weight (LBW) = Males: 50 kg/5 ft + 2.3 kg/in.
Females: 45 kg/5 ft + 2.3 kg/in.

nicardipine have beneficial effects on albumin excretion, while nifedipine has deleterious effects.[4,8,44,46] Alpha-blockers have also been shown to have a beneficial effect on renal function in patients with diabetic nephropathy.[9] Although the angiotensin-II receptor antagonists are too new to have produced convincing data, it is expected that they will have effects similar to ACE inhibitors in those who cannot tolerate ACE inhibitors because of cough, angioneurotic edema, and so forth.[47]

CONCLUSIONS

Given the high rates of end-stage renal disease among type 1 and type 2 diabetic patients, especially among minority groups, the most aggressive approach supported by medical literature should be taken to stem this epidemic. This includes advocacy for diabetes prevention activities and screening and treatment for those patients with microalbuminuria. For the normotensive type 2 diabetic patient with microalbuminuria, the minimal treatment should be aggressive attempts at glycemic control with a goal of Hb A_{1c} of <7.0% in appropriate patients. There is also ample support in the literature for the treatment of these patients with an ACE inhibitor. Blood pressures of >130/85 mm Hg should be considered abnormal, and every attempt should be made to reduce blood pressures to below this reading for all diabetic patients.

Similarly, there is consensus that type 1 diabetic patients with normal blood pressure and persistent microalbuminuria be treated with an ACE inhibitor. Elevations in blood pressure should be treated aggressively with an ACE inhibitor as the initial agent and there is ample support in the literature for aggressive glycemic control with a goal Hb A_{1c} of <7.0%.

It is hoped that these strategies will result in a decrease in the rate of new cases of end-stage renal disease in the future, especially among the minority groups that are the most affected.

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