Diabetic nephropathy is characterized by proteinuria and progressive kidney failure. Hypertension frequently accompanies this scenario. According to the latest figures for the United States, there were ~373,000 patients with end-stage renal disease (ESRD) in 2000, and 45% of new cases resulted from diabetic nephropathy. The absolute number and proportion of kidney failure cases caused by diabetes is expected to rise dramatically as the number of people with diabetes doubles over the next decade because of an epidemic of obesity.

Type 2 diabetic patients have a cardiovascular risk equivalent to nondiabetic individuals with a previous acute myocardial infarction.2 More importantly and often poorly appreciated, diabetic patients with early diabetic nephropathy (proteinuria or a minimally elevated serum creatinine >1.5 mg/dl) have an even greater cardiovascular risk.3 The degree of proteinuria correlates with this risk so that patients with macroalbuminuria have an even higher risk for coronary events than those with microalbuminuria. Abnormalities in vitamin D, parathyroid hormone, and calcium metabolism in patients with even moderate kidney failure lead to vascular and particularly coronary calcification, and this surely contributes to the high incidence of cardiovascular events. Once a patient reaches ESRD, the average survival on dialysis in the United States is 4–5 years, with death generally resulting from cardiovascular events or infection.1

The estimated annual cost for dialysis in a diabetic patient in 1998 was $51,000, which is $12,000 more than that for a nondiabetic patient. Diabetic dialysis patients and transplant recipients also have higher mortality and morbidity rates than their nondiabetic counterparts.1 Therefore, it is extremely important to recognize and treat diabetic nephropathy early. Early referral of patients with diabetic renal disease to a nephrologist is also recommended, because delay has been shown to increase morbidity and mortality.5

The course of diabetic nephropathy is similar in type 1 and type 2 diabetes, although the diagnosis of type 2 diabetes is frequently delayed because of its insidious nature, giving the appearance of an earlier onset of nephropathy in type 2 diabetes. Microalbuminuria predicts the progression to diabetic nephropathy in 80% of untreated patients with type 1 diabetes and is rarely seen when patients have been diagnosed <5 years. Macroalbuminuria generally develops within 10 years, followed by a progressive rise in serum creatinine, eventually leading to ESRD requiring dialysis or transplantation. In contrast, microalbuminuria is commonly seen in patients with type 2 diabetes at the time of diabetes diagnosis or shortly thereafter and signifies vascular endothelial injury and increased cardiovascular risk.6 It is considered more a feature of the insulin resistance syndrome,7 and only 20–40% of these patients will progress to macroalbuminuria and kidney failure. The diagnosis of type 2 diabetes at an older age also leaves less time for ESRD to develop.

Diabetic patients with kidney failure or proteinuria who do not have retinopathy may not have diabetic nephropathy but other glomerular diseases, renal artery stenosis, or small vessel arteriosclerosis. Thus, a renal biopsy may be necessary to obtain a definitive diagnosis in these patients.

Screening for Diabetic Nephropathy
Screening for diabetic nephropathy involves the detection of early proteinuria and kidney failure.

Proteinuria
Most commonly, proteinuria is detected using a standard urine dipstick. Unfortunately, this method is extremely insensitive and may be negative in the face of protein excretion rates up to 10 times the normal value, particularly in dilute urine. Newer reagent strips capable of detecting much lower levels of albumin give results that also vary with urine concentration. Twenty-four-hour or other timed urine collections for measurement of protein or albumin are particularly unreliable in diabetic patients, who often have autonomic neuropathy and incomplete bladder emptying. Thus,
proteinuria be performed when type 2 diabetes is first diagnosed and 5 years after the diagnosis of type 1 diabetes. At least annual measurements are recommended thereafter, but more frequent evaluation of the albumin-to-creatinine ratio can be helpful to direct therapy in patients who have elevated values.

Kidney Failure
In clinical practice, progressive kidney failure is often unrecognized until a patient has lost more than 50% of normal kidney function. This is in part because of the lack of an easy method of measuring glomerular filtration rate (GFR) in clinical settings. The plasma creatinine, measured urinary clearance of creatinine, and estimated creatinine clearance are all used to approximate kidney function in patients.

Unfortunately, creatinine, an end product of muscle metabolism, is both filtered and secreted by the kidney, and

<table>
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<tr>
<th>Category</th>
<th>24-hour collection (mg/24 hours)</th>
<th>Timed collection (µg/min)</th>
<th>Spot collection (mg/g creatinine)</th>
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thus creatinine clearance overestimates true glomerular filtration, particularly when the GFR is <25 ml/min. In addition, the plasma creatinine level is dependent on muscle mass, which in turn relates to sex and age. A small increase in plasma creatinine in early kidney failure, when values range between 0.8 and 2.0 mg/dl, indicates a large drop in kidney function. Therefore, plasma creatinine alone, particularly when the value is within or near the normal range, may mislead clinicians to believe that a patient has normal kidney function. Thin, elderly women are most prone to this misinterpretation.

Twenty-four–hour urine collections for creatinine clearance have most commonly been used to assess kidney function in clinical practice, but errors in obtaining complete and accurate collections, particularly in diabetic patients, who often have autonomic neuropathy and incomplete bladder emptying, make this method unreliable. Thus, the nephrology community now recommends the estimation of creatinine clearance as the most reliable practical measure of kidney function in clinical practice. There are several available formulae, but that formulated by Cockcroft and Gault (Figure 1) is most widely used and accounts for body size, sex, and age.

However, the use of this formula to estimate creatinine clearance is only valid when serum creatinine is relatively stable. It is invalid in acute or subacute renal failure, when serum creatinine is changing rapidly.

In summary, screening for diabetic nephropathy is best achieved by measuring the albumin-to-creatinine ratio in spot urine samples and estimating creatinine clearance from serum creatinine and other known patient characteristics.

Pathogenetic Mechanisms
Many mechanisms have been postulated in the pathogenesis of diabetic nephropathy. These mechanisms appear to be additive in producing the kidney injury, although individuals may vary widely in their susceptibility to such mechanisms. A genetic basis probably accounts for the variable susceptibility.

Systemic hypertension is often associated with the development of nephropathy. The resulting intraglomerular hypertension leads to hyperfiltration that is commonly seen in early uncontrolled human diabetes. This is thought to be an important cause of the progressive kidney damage in both animals and humans. A particularly striking case of a diabetic patient with unilateral renal artery stenosis illustrates this. The kidney on the stenotic side, presumably protected from systemic hypertension, showed no evidence of diabetic nephropathy. On the other hand, the contralateral kidney that received the full force of the blood pressure showed marked changes of diabetic kidney disease. Additional evidence comes from numerous antihypertensive clinical trials that show a beneficial effect in lowering systemic blood pressure and possibly a superior effect of agents that preferentially lower intraglomerular pressure by blocking the renin angiotensin system.

Proteinuria, a hallmark of diabetic nephropathy, appears to contribute to kidney damage possibly through release of inflammatory cytokines in the kidney interstitium. Many kidney diseases appear to progress more rapidly if patients have marked proteinuria. Additionally, almost all therapies that slow the progression of kidney disease also reduce proteinuria.

Hyperglycemia is also associated with the development and more rapid progression of diabetic nephropathy. Several studies in both type 1 and, to a lesser extent, type 2 diabetic patients have shown that kidney disease occurs more commonly when the hemoglobin A1c (A1C) is >7%. In another study of patients with diabetic nephropathy who received a pancreatic transplant alone, normalizing blood glucose resulted in regression to normal renal pathology over 10, but not 5, years.

Hypercholesterolemia may contribute to the progression of kidney disease, as shown in a study of type 1 diabetic patients with nephropathy whose risk for progression was higher if their plasma total cholesterol was >220 mg/dl.

Diabetic patients who smoke cigarettes appear to have a greater chance of developing kidney disease, although the mechanism is unclear. Increased protein intake in both animals and humans leads to an increase in GFR. Animal experiments show that this is because of intraglomerular hypertension, which in turn results in glomerular injury. Whether this mechanism plays a part in human disease is less clear, although there is anecdotal evidence of rapid progression of kidney failure in patients on a popular high-protein diet.

Genetic factors are implicated in the pathogenesis of diabetic nephropathy. The renin-angiotensin aldosterone system appears to play a major role in the development of diabetic nephropathy, presumably by affecting hemodynamic and nonhemodynamic factors within the glomeruli. Relating to this, the insertion/deletion polymorphism of the angiotensin-converting enzyme (ACE) gene appears to determine whether individual patients will develop diabetic nephropathy, their rate of progression, and their response to therapy. The DD genotype appears particularly vulnerable. Diabetic patients whose immediate family members have hypertension or kidney disease, diabetic or otherwise, appear particularly prone to diabetic nephropathy.

**Figure 1. The Cockcroft-Gault formula for estimating creatinine clearance.**

\[
\text{Estimated creatinine clearance} = \left( \frac{140 - \text{age}}{\text{weight in kg}} \times \frac{\text{Plasma creatinine}}{72} \right)
\]

*For females, this value is further multiplied by 0.85.*
Type 2 diabetic African Americans, Mexican Americans, and Native Americans such as the Pima Indians have a three- to sixfold increased risk of developing nephropathy compared to type 2 diabetic whites. The presumably different genotypes in these populations suggest a causative role for socioeconomic factors such as obesity, diet, and poorly controlled blood glucose and blood pressure. African Americans are at greater risk for developing other kidney diseases, and it has been suggested that a congenitally lower nephron number places the kidneys of African Americans at higher risk.

**Primary Prevention**

Primary prevention is applied to patients without evidence of kidney injury and in whom albuminuria and kidney function are normal. Hypertension may or may not be present. Most clinical studies have focused on the use of antihypertensive agents and achieving better glycemic control because these are the two most readily applicable treatment strategies.

**Antihypertensive Therapy**

Several small clinical trials comparing ACE inhibition to placebo in normotensive type 1 and type 2 diabetic patients with normal urinary albumin excretion showed that ACE inhibition lowered the risk of developing microalbuminuria. Other studies in hypertensive, normoalbuminuric type 2 diabetic patients have compared the effect of ACE inhibition with long-acting dihydropyridine calcium entry-blockers or β-blockers. Each demonstrated a similar beneficial effect in providing protection against the development of renal injury. No studies are yet available using angiotensin II receptor–blocking agents for primary prevention of diabetic nephropathy in type 1 or type 2 diabetes.

**Blood Glucose Control**

A meta-analysis of seven randomized studies in type 1 diabetes showed that patients receiving intensive insulin therapy were less likely (odds ratio: 0.34) to have an increase in urinary albumin excretion than patients receiving conventional therapy. In the Diabetes Control and Complications Trial (DCCT), 1,441 patients with type 1 diabetes, half of whom had mild retinopathy initially, were randomized to intensive (achieved A1C results of 7.0%) and conventional (A1C results of 9.6%) insulin therapy and followed for a mean of 6.5 years. Ninety-five percent of patients had normal urinary albumin excretion at the beginning of the study. Intensive therapy reduced the risk of developing microalbuminuria by 34% in patients without retinopathy and by 43% in patients with retinopathy. Macroalbuminuria was reduced by 56%. Importantly, 16% of patients without retinopathy treated with intensive insulin therapy still developed microalbuminuria after 9 years. Therefore, achieving glycemic control to this degree with at least three injections of insulin daily is not sufficient in itself to prevent diabetic nephropathy. A Japanese randomized study similar in design to the DCCT involved 110 type 2 diabetic patients followed for up to 6 years. The risk of developing nephropathy in the well-controlled group (A1C: 7.1%) was 70% lower compared to that of poorly controlled patients (A1C: 9.4%). This finding in type 2 diabetes has been confirmed by the U.K. Prospective Diabetes Study, in which a 0.9% reduction in A1C was associated with a 34% reduction in the development of albuminuria over 12 years.

**Treatment of Diabetic Nephropathy**

**Blood Pressure Control**

Antihypertensive therapy has been shown to be beneficial in both type 1 and type 2 diabetic patients with nephropathy. Blood pressure goals have been set by both the ADA and the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. For diabetic patients in general, the target blood pressure is >130/80 mmHg. The target is even more stringent, >120/75 mmHg, for patients who have >1 g proteinuria.

Blockade of the renin-angiotensin system with either ACE inhibition or angiotensin II receptor blockade is the first line of therapy for several reasons. It has been shown to selectively decrease efferent arteriolar resistance in the kidney and thus decrease the intraglomerular hypertension that is as an important mechanism for kidney injury in diabetes. There may also be direct effects of these agents on the permeability characteristics of the glomeruli that could in part explain their antiproteinuric effects.

ACE inhibitors have a well-documented cardioprotective effect in diabetic and nondiabetic patients with known ischemic heart disease, particularly in those patients with congestive heart failure (CHF) or post-myocardial infarction. This is an extremely important consideration in type 2 diabetic individuals who are considered to have a coronary heart disease equivalent and often have asymptomatic CHF and left ventricular hypertrophy. There is even evidence that use of an ACE inhibitor in nondiabetic subjects may lower the risk of developing diabetes by some 30%, and this is also true of the angiotensin II receptor–blocking agent losartan (Cozaar) when compared to atenolol (Tenormin). ACE inhibitors are recommended as first-line therapy in type 1 diabetes. There is a wealth of evidence to show kidney protection and preservation in type 1 diabetic patients when proteinuria with or without renal failure is present. So far, there is little evidence in type 1 diabetes that angiotensin II receptor blockers prevent or slow the course of kidney failure. They have been shown in short-term studies to decrease proteinuria, and they may eventually be found to have similar long-term outcome benefits to those seen with the ACE inhibitors, but these studies are still underway.

In contrast, because of two recent studies of angiotensin II receptor blockade in type 2 diabetic patients with nephropathy, these agents are now sug-
gested as first-line therapy for nephropathy in these patients. Both these studies, each with more than 1,500 patients randomized and placebo-controlled, showed reductions of ~30% in ESRD over 3 years. Neither study had the statistical power to demonstrate a benefit in cardiovascular mortality and morbidity. ACE inhibitors, on the other hand, have not shown any renal protective advantage in type 2 diabetes over other antihypertensive agents such as β-blockers or nondihydropyridine calcium-channel blockers (CCBs).35,36

Controversy therefore remains in type 2 diabetes regarding whether ACE inhibitors with their proven cardiovascular protection should take second place to angiotensin II receptor–blockers with their kidney protection, as recommended in the latest ADA guidelines.9 Given the extremely high cardiovascular risk in these patients, the author continues to prescribe ACE inhibitors initially, using angiotensin II receptor blocking agents only when cough or angioedema develops.

There is, however, a theoretical benefit and indeed some clinical evidence that combining ACE inhibitors and angiotensin II receptor blockers may be more effective than using either agent alone in reducing both proteinuria and blood pressure.37 The immediate rise in serum creatinine following treatment with an ACE inhibitor, an angiotensin II receptor blocker, or, for that matter, any agent that lowers systemic blood pressure is often misunderstood. This serum creatinine elevation is usually related to a decrease in renal perfusion resulting in a lower intraglomerular capillary pressure and may therefore be beneficial, slowing renal injury in the long term.

Analysis suggests that the greater the initial rise in serum creatinine, the smaller the eventual decline in renal function.38 However, a large initial serum creatinine elevation should alert clinicians to the possibility of underlying bilateral renal artery stenosis. Another potential adverse effect seen with renin-angiotensin blockade is hyperkalemia, and serum potassium must be monitored closely, particularly in patients whose kidney function is deteriorating or when a β-blocker or spironolactone (Aldactone) is being used.

Most importantly, clinicians must realize that a single antihypertensive agent, whether an ACE inhibitor or an angiotensin II receptor blocker, is inadequate to achieve blood pressure goals in most patients with hypertension and kidney disease. In an analysis of five recent clinical hypertension trials, a combination of three antihypertensive medications on average was required to reach goal blood pressure.38 Some patients may need five or more medications with different antihypertensive mechanisms of action to achieve adequate control.

Which antihypertensive to add to an ACE inhibitor or angiotensin II receptor blocker is unclear and depends on the individual patient.

Regarding CCBs, the nondihydropyridines verapamil (Calan, Isoptin, Vere- lan, Covera-HS) and diltiazem (Dilacor, Tiazac, Cardizem) may be indicated over the dihydropyridine CCBs nifedipine (Procardia, Adalat), amldipine (Norvasc), felodipine (Plendil), nisoldipine (Sular), and others. The nondihydropyridine CCBs, but not the dihydropyridines, lower proteinuria in humans and prevent adverse renal pathological effects in animal studies. The reduction in proteinuria is additive when an ACE inhibitor and a nondihydropyridine CCB are used in combination.39 Clinical studies of renal protection show benefit with nondihydropyridine agents,40 but a majority of the studies with dihydropyridines show no advantage compared to placebo.34,35 However, when an antihypertensive regimen includes a β-blocker and a CCB, a dihydropyridine CCB must be used because a nondihydropyridine/β-blocker combination may produce clinically significant brady-arrhythmias. Interestingly, a recent retrospective study of more than 3,700 diabetic patients on dialysis showed that patients on CCBs, dihydropyridine or nondihydropyridine, had a 21% lower risk of all-cause mortality and a 26% lower risk of cardiovascular mortality.41

Clinicians often avoid using β-blocking agents in diabetic patients because of the misconception that these drugs have an adverse effect on blood glucose control or may mask the symptoms of hypoglycemia. A recent analysis of the literature indicates that β1-selective agents do not have a significant adverse effect on glucose metabolism, nor do they prolong hypoglycemia or mask hypoglycemic symptoms.42

They have been shown to be renoprotective in type 141 and type 2 diabetes,22 lowering proteinuria and slowing the progression of kidney failure. Considering the cardiovascular benefits in these patients who often have asymptomatic heart failure or ischemic cardiomyopathy, the combination of an ACE inhibitor and β-blocker may be ideal.

There may also be an advantage to using carvedilol (Coreg), a nonselective β-blocker with α-blocking properties, over conventional β-blockers. It increases insulin sensitivity,44 improves glycemic control,45 and dyslipidemia,46 and has marked antioxidant properties in contrast to atenolol and metoprolol (Lopressor, Toprol XL).

Other classes of antihypertensive agents included diuretics, centrally acting α-agonists, peripheral α1-blocking agents, and vasodilators. Diuretics, particularly thiazides, are very effective at lowering blood pressure when used alone or in combination with ACE inhibitors or angiotensin II receptor blockers, but they may adversely affect the lipids. α1-Blockers increase the risk of cardiovascular mortality when used alone and must therefore be used with caution. Centrally acting α-agonists can be extremely effective as an addition in resistant patients, although noncompliant patients may have rebound hypertension when they miss an oral dose.

The author uses minoxidil (Loniten) as a last resort when a patient is already taking drugs from four or more different antihypertensive classes with inadequate control. Severe fluid retention including
pleural and pericardial infusions may be seen with this agent.

**Blood Glucose Control**
Up to half of newly diagnosed uncontrolled type 1 diabetic patients have high GFRs. Early studies in which near-normal blood glucose control was achieved for several days demonstrated a reduction in GFR to normal. Controlled trials of glycemic control with long-term follow-up in type 1 diabetes are conspicuously absent. However, previously mentioned studies in type 1 diabetic patients with biopsy-proven nephropathy who received a pancreatic transplant showed almost complete histological resolution at 10 years’ follow-up. This suggests that reversal of pathology is possible when normoglycemia is achieved and maintained over a long period of time.

**Restriction of Protein Intake**
Ingestion of a large protein load in both animal and human subjects causes a significant increase in GFR. This hyperfiltration and presumed intraglomerular hypertension causes injury to the kidney and exaggerates the GFR decline in diabetic nephropathy. Although results of clinical trials involving protein intake restriction have not always shown benefit, two small controlled studies have demonstrated a significantly slower decline in GFR when protein and phosphate intake are decreased.

**Multifactorial Treatment**
No controlled trials have compared individual interventions with therapy attempting to address multiple risk factors simultaneously. However, one study showed that therapy targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria in patients with type 2 diabetes significantly slowed the progression of nephropathy.

**Conclusion**
Diabetic nephropathy manifested by proteinuria and progressive kidney failure, often accompanied by hypertension, indicates heightened cardiovascular risk and therefore requires early diagnosis and treatment.

Screening is best achieved by measurement of the urinary albumin-to-creatinine ratio in an untimed urine sample and estimation of creatinine clearance from serum creatinine using the Cockcroft-Gault formula. These should be done at the time of diagnosis of type 2 diabetes and not more than 5 years following the diagnosis of type 1 diabetes.

Aggressive treatment to recommended goals is required for hypertension (<130/80 or <120/75 mmHg if microalbuminuric), hyperglycemia (A1C <7%), and hypercholesterolemia (LDL cholesterol <100 mg/dl). Repeated measurements of urinary albumin-to-creatinine ratio may also be used to assess the effectiveness of therapy.

Multi-drug therapy is often necessary, particularly for controlling hypertension. Blockade of the renin-angiotensin system is the first step in antihypertensive therapy for diabetic patients, and consideration should be given to the effect on metabolic control, insulin resistance, and cardiovascular risk when adding further agents. The nonselective β/α-blocker carvedilol, a nondihydropyridine CCB, or a thiazide diuretic is added sequentially, followed by other agents. The serum creatinine rise seen when initiating antihypertensive therapy is not a concern unless >1.0–1.5 mg/dl.

Restricted intake of protein (0.8 g/kg/day) and phosphorus (600 mg/day) should be considered in patients with progressive kidney failure. Smoking must be discouraged, and nephrotoxic agents such as contrast dye and nonsteroidal anti-inflammatory agents, including Cox 2 inhibitors, must be avoided.

Early referral to a nephrologist when estimated creatinine clearance is <60 ml/min is recommended to allow adequate time to prepare for renal replacement therapy, dialysis, or transplantation, resulting in lower morbidity and mortality.

**REFERENCES**


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