Diabetic Nephropathy: Common Questions

MICAH L. THORP, D.O., M.P.H., *Lake Road Nephrology Clinic, Milwaukie, Oregon*

Diabetic nephropathy, or diabetic kidney disease, affects 20 to 30 percent of patients with diabetes. It is a common cause of kidney failure. Diabetic nephropathy presents in its earliest stage with low levels of albumin (microalbuminuria) in the urine. The most practical method of screening for microalbuminuria is to assess the albumin-to-creatinine ratio with a spot urine test. Results of two of three tests for microalbuminuria should be more than 30 mg per day or 20 mcg per minute in a three- to six-month period to diagnose a patient with diabetic nephropathy. Slowing the progression of diabetic nephropathy can be achieved by optimizing blood pressure (130/80 mm Hg or less) and glycemic control, and by prescribing an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Patients with diabetes and isolated microalbuminuria or hypertension benefit from angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. In the event that these medications cannot be prescribed, a nondihydropyridine calcium channel blocker may be considered. Serum creatinine and potassium levels should be monitored carefully for patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. These medications should be stopped if hyperkalemia is pronounced. (Am Fam Physician 2005;72:96-99,100.

▶ **Patient information:** A handout on diabetic nephropathy, written by the author of this article, is provided on page 100.

Approximately one fourth to one third of patients with diabetes develop renal manifestations. Because of the large prevalence of diabetes in the general population, diabetes has become the leading cause of end-stage renal disease in the United States.[1] There is good evidence that early treatment delays or prevents the onset of diabetic nephropathy, or diabetic kidney disease. A variety of issues and specific questions often arise in the management of diabetic nephropathy. This article addresses some of the common questions raised by physicians managing patients with this disease.

Diagnosis of Diabetes with Renal Manifestations

Diabetic nephropathy presents in its earliest stage with low levels of albumin (microalbuminuria) in the urine. This often is referred to as incipient nephropathy. As the disease progresses, urine albumin levels increase until the patient develops overt nephropathy (defined as more than 300 mg per 24 hours or more than 200 mcg per minute). Overt nephropathy often occurs in conjunction with a hyperfiltrative period, in which the creatinine clearance and glomerular filtration rate are high. The elevated clearance is deceptive, however, because it is followed by a gradual decrease in glomerular filtration rate that ultimately leads to kidney failure.[2]

Microalbuminuria rarely develops in patients with type 1 diabetes during the first few years of the disease. For this reason, the American Diabetes Association (ADA) recommends that screening begin only after the patient has had type 1 diabetes for five years.[3]

Because of the long duration of abnormal glucose metabolism that often precedes diagnosis, patients with type 2 diabetes are more likely to have microalbuminuria (or overt nephropathy) at diagnosis. Thus, patients with type 2 diabetes should be screened at the time of diagnosis for the presence of microalbuminuria.[3]

STRENGTH OF RECOMMENDATIONS

Key clinical recommendation	*Label*	*References*
Hypertensive patients with diabetes and microalbuminuria should be given ACE inhibitors to protect the kidneys by reducing the albumin excretion rate.	A	16
Patients who receive ACE inhibitors or angiotensin receptor blockers should have their serum potassium levels monitored for hyperkalemia.	C	19

ACE = angiotensin-converting enzyme.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, opinion, or case series. For more information about the SOR evidence rating system, see page 15 or http://www.aafp.org/afpsort.xml.

Screening for microalbuminuria can be accomplished in a variety of ways. The three approaches most commonly used are measurement of albumin-to-creatinine ratio on a spot urine test, albumin from a 24-hour urine collection, and albumin from a timed collection (e.g., 10 hours overnight). The ratio from spot urine is obtained most easily, and collection errors occur less frequently. A ratio of more than 30 mg albumin per 1 g creatinine is considered elevated on a spot urine test. Urinary albumin of more than 30 mg per 24 hours is diagnostic on a timed sample. Transient elevations of microalbuminuria can be caused by exercise, urinary tract infections, hyperglycemia, febrile illness, severe hypertension, or heart failure. Abnormal results should be confirmed with repeated testing. The ADA guidelines suggest that two of three tests for microalbuminuria need to be positive in a three- to six-month period to diagnose diabetic nephropathy correctly.[3]

Patients with overt nephropathy do not need screening for microalbuminuria because the level of protein in the urine is high enough to be detected easily on routine urinalysis.

Definitive Treatment of Diabetic Nephropathy

As with most complications of diabetes, there is no definitive "cure" for diabetic nephropathy. However, a recent study[4] followed nearly 400 patients with type 1 diabetes and microalbuminuria for six years, and more than one half of the patients in the study experienced regression of microalbuminuria. This suggests that not all patients with microalbuminuria progress to diabetic nephropathy. Patients with low systolic blood pressure, low levels of cholesterol, and low levels of glycosylated hemoglobin were more likely to experience regression.

Management of Diabetes with Renal Disease

Slowing the progression of diabetic nephropathy includes optimizing glycemic control (as demonstrated by the United Kingdom Prospective Diabetes Study[5] [UKPDS] and the Diabetes Control and Complications Trial[6]), controlling hypertension, and using angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). More controversial interventions include the use of a protein-restricted diet for patients with type 1 diabetes[7] and nondihydropyridine calcium channel blockers in the event that ACE inhibitors or ARBs cannot be used for patients with microalbuminuria or nephropathy. Dihydropyridine calcium channel blockers are not effective.[3]

The American Diabetes Association recommends screening for microalbuminuria in patients with type 1 diabetes only after the patient has had the disease for five years.

On the basis of the trials mentioned above, hemoglobin A1C levels should be kept at less than 7 percent.[8] Ideal blood pressure measurements are unclear, but on the basis of the UKPDS[5] and Hypertension Optimal Treatment studies,[9] a reasonable blood pressure target is 130/80 mm Hg or less. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment

of High Blood Pressure recommends this target,[10] as does the National Kidney Foundation.[11] There is much evidence to show that ACE inhibitors slow the progression of diabetic nephropathy in patients with type 1 diabetes,[12,13] and some evidence that the progression is slowed in patients with type 2 diabetes exists as well.[14] Results of the Reduction of Endpoints in NIDDM (non–insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan study[15] and the Irbesartan Diabetic Nephropathy Trial[16] showed that ARBs slow the progression of diabetic nephropathy significantly in patients with type 2 diabetes. If one class cannot be tolerated, the other may be substituted.[8]

Patients with type 2 diabetes should be screened at the time of diagnosis for the presence of microalbuminuria.

Prescribing ACE Inhibitors or ARBs

NORMOTENSIVE WITH MICROALBUMINURIA OR HYPERTENSIVE WITHOUT MICROALBUMINURIA

Studies have shown that ACE inhibitors and ARBs are beneficial in reducing the progression of microalbuminuria in normotensive patients with type 1 diabetes[17] and in normotensive patients with type 2 diabetes.[3,18]

Patients with hypertension and diabetes clearly benefit from lowering of blood pressure, regardless of the presence of nephropathy. A number of studies suggest that a variety of agents may be appropriate first-line treatments for blood pressure. Because ACE inhibitors and ARBs have been shown to decrease or slow the progression of complications in diabetes, it seems reasonable to use a medication from one of these two classes of antihypertensive drugs as a first-line agent in hypertensive patients who have diabetes without microalbuminuria.[8,14,19]

ELEVATED SERUM CREATININE

There is no specific creatinine level beyond which ACE inhibitors or ARBs cannot be used. Patients with more advanced nephropathy may experience greater benefits from these medications than patients with mild nephropathy.

A review[20] of 12 randomized clinical trials evaluating renal disease progression in patients with preexisting renal insufficiency found a strong association between acute increases in serum creatinine levels of up to 30 percent that stabilize within the first two months of ACE inhibitor therapy and long-term preservation of kidney function.

With this in mind, patients who initiate ACE inhibitor (and presumably ARB) therapy should have creatinine levels checked shortly after starting the medication, and serum potassium levels should be monitored for hyperkalemia while the patient receives the medication.[19]

Other Antihypertensive Choices

A number of small studies[21] have demonstrated that nondihydropyridine calcium channel blockers can reduce albuminuria. These studies fail to show a reduction in the rate of decrease of glomerular filtration rate with their use.

Author disclosure: Nothing to disclose.

The Author

MICAH L. THORP, D.O., M.P.H., is a nephrologist at the Kaiser Kidney Program's Lake Road Nephrology Center, Portland, Ore. He received his osteopathic degree at the University of Des Moines in Iowa, and his master's degree in public health from Oregon Health and Sciences University, Portland. Dr. Thorp completed a residency in internal medicine at St. Vincent's Medical Center, Portland, and a fellowship in nephrology at Oregon Health and Sciences University.

Address correspondence to Micah L. Thorp, D.O., M.P.H., Lake Road Nephrology Clinic, 6902 SE Lake Rd., Milwaukie, OR 97267 (e-mail: micahthorp@comcast.net). Reprints are not available from the author.

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