REVIEW

CME CREDIT

CHRISTOPHER J. HEBERT, MD
Louis Stokes Cleveland VA Medical Center,
Cleveland, Ohio

Preventing kidney failure: Primary care physicians must intervene earlier

ABSTRACT

Mild chronic kidney disease often goes unnoticed until a substantial loss of renal function has occurred. Given the increasing incidence of chronic kidney disease, primary care physicians play a critical role in the early evaluation and intervention of patients at risk. This article discusses the key steps, with emphasis on patients with mild disease due to diabetes or hypertension.

KEY POINTS

The serum creatinine concentration is an insensitive test for mild chronic kidney disease; one should calculate the glomerular filtration rate in patients at risk.

Proteinuria is both a strong predictor of outcomes and a modifiable risk factor for chronic kidney disease.

The highest priority in managing mild chronic kidney disease is to control the blood pressure optimally. The standard goal is less than 130/80 mm Hg, but 125/75 is suggested for patients with heavy proteinuria.

Angiotensin-converting enzyme inhibitors are renoprotective in diabetic and nondiabetic kidney diseases; angiotensin-receptor blockers are renoprotective in type 2 diabetes.

Tight glycemic control for diabetic patients and avoidance of cigarette smoking are of critical importance in chronic kidney disease.

IF WE HOPE to make a dent in the rising epidemic of kidney failure, primary care physicians need to get more involved in detecting and managing chronic kidney disease in its early stages. So many people are at risk that nephrologists cannot do the job alone.

The task need not be daunting. Five simple questions can help one to intervene early and effectively, using just a few minutes of an office visit:

- Is the patient at risk of developing chronic kidney disease?
- If the patient is at risk, does his or her kidney show signs of damage, as measured by the glomerular filtration rate (GFR)?
- Is proteinuria present, and if so, how can it be minimized?
- If chronic kidney disease is present, has the target blood pressure of less than 130/80 mm Hg been attained?
- Is an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) indicated?

To improve the care of patients in the early stages of kidney disease, the National Kidney Foundation has issued clinical practice guidelines.[1] My review draws heavily but not exclusively from their report.

CHRONIC KIDNEY DISEASE IS EPIDEMIC

In the United States:

- More than 372,000 patients required renal replacement therapy (chronic dialysis or transplantation) in 2000, and the number is rising.[2]
- An estimated 10.9 million patients have

TABLE 1

Stages of chronic kidney disease

STAGE	DESCRIPTION	GFR (ML/MINUTE)
1	**Kidney damage with normal GFR**	≥ 90
2	**Mild kidney disease**	60–89
3	**Moderate kidney disease**	30–59
4	**Severe kidney disease**	15–29
5	**Kidney failure**	< 15, or on renal replacement therapy

FROM LEVEY AS, CORESH J, BOLTON K, ET AL. K/DOQI CLINICAL PRACTICE GUIDELINES FOR CHRONIC KIDNEY DISEASE: EVALUATION, CLASSIFICATION, AND STRATIFICATION. KIDNEY DISEASE OUTCOME QUALITY INITIATIVE. AM J KIDNEY DIS 2002; 39(SUPPL 2):S1–S246.

chronically elevated serum creatinine levels, but their renal function is not low enough to require renal replacement therapy.[3]

- An unknown number of people, but a number that is thought to be growing at an alarming rate, has either decreased renal function despite normal serum creatinine levels or kidney damage without a decrease in function. Most notable are people with proteinuria. A physician can easily fail to recognize this condition, thereby denying such a patient proven renoprotective therapies.

Patients at risk for kidney disease need further evaluation

IS THE PATIENT AT RISK?

The National Kidney Foundation[1] has identified the following as "potential risk factors for susceptibility to and initiation of chronic kidney disease," and calls for further evaluation if these are present.

- Advanced age
- Non-Caucasian race
- Exposure to certain chemical and environmental conditions
- Low income or education level
- Diabetes
- Hypertension
- Autoimmune diseases
- Systemic infections
- Urinary tract infections
- Urinary stones
- Lower urinary tract obstruction
- Neoplasia
- Family history of chronic kidney diseases
- Recovery from acute kidney failure
- Reduction in kidney mass
- Exposure to nephrotoxic drugs
- Low birth weight.

To this list I would add:

- Obesity
- Cigarette smoking
- Hyperlipidemia
- Illicit drug use (eg, heroin).

Furthermore, a more rapid decline in renal function can be predicted for patients with higher blood pressure,[4] poor glycemic control,[5] or proteinuria.[6,7]

WHAT IS CHRONIC KIDNEY DISEASE? THE NEW STAGING SYSTEM

Until recently, there was no specific and standard definition of chronic kidney disease, which likely contributed to the limited role that early detection and prevention plays in the primary care practice.

However, the National Kidney Foundation has devised a new staging system for chronic kidney disease,[1] which may help health care providers address the issue with more precision. In this system, the GFR is used to define five levels of disease (TABLE 1).

- **Stage 1** is kidney damage with a normal GFR (≥ 90 mL/minute). This would often be detected by the presence of proteinuria.
- **Stage 2** is kidney damage with mildly decreased kidney function (GFR 60–89 mL/minute).
- **Stage 3** is moderately decreased kidney function (GFR 30–59 mL/minute)
- **Stage 4** is severely decreased kidney function (GFR 15–29 mL/minute)
- **Stage 5** is kidney failure (end-stage renal disease) with a GFR less than 15 mL/minute.

These stages can be used to guide treatment of the patient and referral to a nephrologist.

Kidney biopsy is usually not necessary for newly diagnosed chronic kidney disease, particularly in the setting of long-standing diabetes or hypertension. However, referral for biopsy may be considered in the presence of the nephrotic syndrome, collagen vascular disease, hematuria with a structurally normal urinary tract, or rapid worsening of GFR or proteinuria.

IS THE KIDNEY DAMAGED? USE GFR, NOT CREATININE ALONE

If the patient has any of the risk factors listed above, the next step is to determine if he or she has chronic kidney disease.

Serum creatinine is not enough

The serum creatinine concentration is a convenient and inexpensive method of assessing renal function, and a consistently elevated level reliably indicates chronic kidney disease.

However, serum creatinine is a poor screening test for mild disease, and some patients have a substantial decrease in GFR while their serum creatinine remains within the normal range. This is most common in the elderly, those with low muscle mass, and women.

Therefore, when evaluating a patient at risk for chronic kidney disease, it is important to calculate the GFR, using one of several formulas (TABLE 2).

Calculating the GFR

The MDRD formula (derived from the Modification of Diet in Renal Disease trial) is more accurate than the traditional 24-hour creatinine clearance determination.[8]

This formula may seem hard to use, but it is available in software for desktop or handheld computers, for example, MedCalc for Palm Pilots and on the World Wide Web at **www.kdoqi.org**. Using these, you can calculate the GFR accurately in seconds if you have the appropriate laboratory and demographic data (serum creatinine, sex of the patient, race of the patient, blood urea nitrogen, and serum albumin).

The 24-hour creatinine clearance, based on a 24-hour urine sample, may be less accurate than the MDRD formula but more accurate than the Cockroft-Gault formula. The disadvantages of this method include the added expense and the potential for errors in urine collection.

The Cockroft-Gault formula, although somewhat less accurate, is more familiar than the MDRD formula and can be quickly used during an office visit using a simple calculator; this estimated creatinine clearance is a good approximation of the GFR.[9]

TABLE 2

Three formulas for calculating the glomerular filtration rate (GFR)

MDRD formula (most accurate – calculator at www.kdoqi.org)

$$\begin{aligned} GFR = {} & 170 \times \text{serum creatinine concentration}^{-0.999} \\ & \times \text{age}^{-0.176} \\ & \times 0.762 \text{ (if female)} \\ & \times 1.18 \text{ (if race is black)} \\ & \times \text{blood urea nitrogen concentration}^{-0.17} \\ & \times \text{serum albumin concentration}^{-0.318} \end{aligned}$$

24-hour creatinine clearance
(intermediate accuracy, least convenient)

$$GFR = \frac{\text{urine creatinine concentration} \times \text{volume in mL}}{\text{serum creatinine concentration} \times \text{time in minutes}}$$

Cockroft-Gault formula (least accurate, most convenient)

$$GFR = \frac{(140 - \text{age}) \times \text{weight in kg} \times (0.85 \text{ if female})}{72 \times \text{serum creatinine concentration}}$$

The Cockroft-Gault formula is less accurate for patients over age 65 or at the extremes of body weight.

Of note: none of these three formulas should be used in acute renal failure; a stable serum creatinine concentration is required.

The clearance of an infused substance such as inulin or iothalamate is the gold standard for determination of GFR, but is not practical for primary care physicians.

Calculate the GFR from the creatinine, BUN, and albumin at www.kdoqi.org

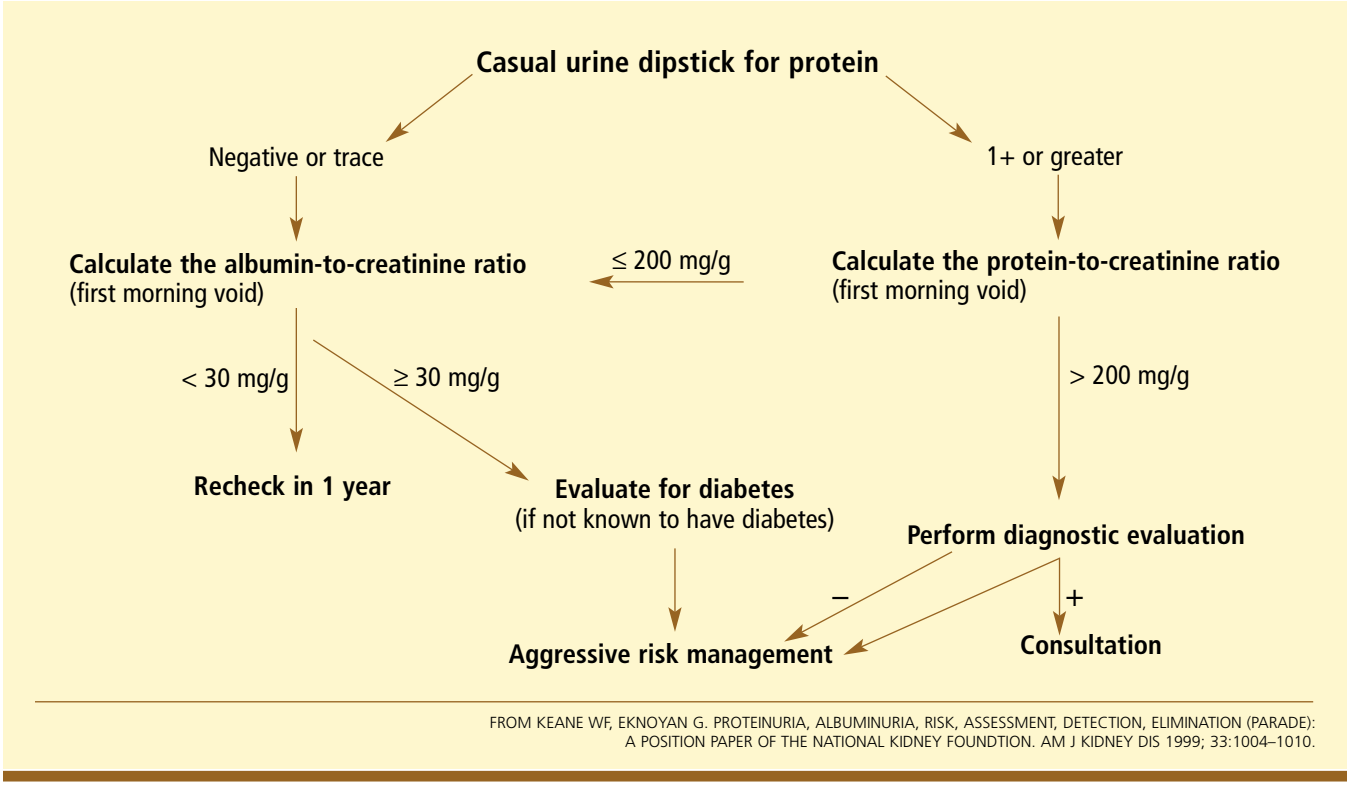
REGARDLESS OF GFR, IS PROTEINURIA PRESENT?

The presence and amount of urinary protein affects the prognosis and is useful in making clinical decisions. Proteinuria is a strong predictor of renal outcomes, it is modifiable, and its reduction is associated with a slowing of the decline in renal function.[6,7]

In addition, experimental evidence supports the notion that proteinuria itself has a toxic effect on the kidney. Interaction of protein with tubular cells can lead to inflammation and fibrosis, which contributes to nephron loss and deterioration in GFR.[7]

A dipstick urinalysis is indicated in patients at risk for chronic kidney disease, regardless of GFR.

Evaluation of proteinuria in patients at risk for cardiovascular or renal disease



FROM KEANE WF, EKNOYAN G. PROTEINURIA, ALBUMINURIA, RISK, ASSESSMENT, DETECTION, ELIMINATION (PARADE): A POSITION PAPER OF THE NATIONAL KIDNEY FOUNDTION. AM J KIDNEY DIS 1999; 33:1004–1010.

FIGURE 1

The prognostic value of dipstick-positive proteinuria (macroproteinuria) has been demonstrated repeatedly. For example, Ruggenenti et al,[10] in the Ramipril Efficacy in Nephropathy study, found that 24-hour urinary protein excretion was the best predictor of progression of disease in patients with nondiabetic chronic nephropathies. Those in the lowest tertile (< 1.9 g/24 hours) had a 4.3% rate of progression to end-stage disease over a median follow-up of 23 months, while those in the highest tertile (> 3.9 g/24 hours) had a rate of 32.5%.

If the patient has dipstick-positive proteinuria

If the patient has dipstick-positive proteinuria of 1+ or more, then one should determine the **urinary protein-to-creatinine ratio** in a first morning sample. This ratio correlates well with the 24-hour protein excretion and is a convenient and inexpensive method of monitoring proteinuria over time and assessing the effect of an intervention.

The 1999 consensus statement PARADE (Proteinuria, Albuminuria, Risk, Assessment, Detection, Elimination)[11] provides guidance on this key issue and a useful algorithm for management of dipstick protein findings (FIGURE 1).

If the patient has negative or trace protein

If the patient has either negative or trace protein by dipstick, then testing for **microalbuminuria** is indicated. This can be done by measuring the **albumin-to-creatinine ratio** in a random urine sample (preferably the first morning void). An elevated ratio (> 30 mg/g), confirmed by repeat testing, is a risk factor for progressive kidney disease and is also a strong risk factor for cardiac disease. Although testing for microalbuminuria annually has been the standard of care in diabetes for years, it remains poorly utilized.

Many experts recommend screening for microalbuminuria in nondiabetic patients at risk for chronic kidney disease or cardiovascular disease, such as in patients with essential

hypertension.[12] Microalbuminuria predicts increased risk for declining renal function and for cardiovascular events in this setting, as it does in diabetes.

For example, Bigazzi et al[13] found that hypertensive patients with microalbuminuria had a higher rate of major cardiovascular events (21.3% vs 2.3%) and a greater decrease in creatinine clearance (12.7 mL/minute vs 7.1 mL/minute) than did those without microalbuminuria during approximately 7 years of follow-up.

If a patient has microalbuminuria, one should start intensive cardiovascular risk factor modification and consider the renoprotective practices discussed below, with the intent of reducing the urine albumin level to normal.

HOW TO MINIMIZE PROTEINURIA

The level of urinary protein excretion can be lowered by any of the interventions listed in TABLE 3, or by combinations of these interventions.

Optimal blood pressure control and ACE inhibitors will go a long way in minimizing proteinuria, but the primary care physician should be aware that other treatments such as specific drug combinations and dietary salt and protein restriction can also substantially decrease even heavy proteinuria.

Both ARBs and nondihydropyridine calcium channel blockers have antiproteinuric effects.

It is important that patients with proteinuria restrict their dietary salt intake. Unrestricted salt intake can virtually eliminate the antiproteinuric effect of an ACE inhibitor.[14]

Although there is evidence supporting dietary protein restriction in the management of proteinuric kidney disease, some controversy exists. The primary care physician may wish to pursue this after consulting a nephrologist.

If proteinuria cannot be kept below 200 mg per day, then referral to a nephrologist may be indicated.

IS THE BLOOD PRESSURE < 130/80?

The highest priority for the primary care physician in managing mild chronic kidney disease is to control the blood pressure optimally.

The standard goal is less than 130/80 mm Hg, but 125/75 is suggested for patients with heavy proteinuria,[15] and some experts advise that the blood pressure be kept as low as tolerated for this subset of highest-risk patients.

The patient should be aware that reaching this target slows the rate of decline in renal function substantially, and that many patients who achieve and maintain this goal do so by combining a healthy lifestyle with the use of multiple antihypertensive drugs.

TABLE 3

Interventions that decrease proteinuria

Blood pressure control

Medications
- Angiotensin-converting enzyme (ACE) inhibitors
- Angiotensin-receptor blockers (ARBs)
- Nondihydropyridine calcium channel blockers

Dietary salt restriction

Dietary protein restriction

RENOPROTECTIVE DRUGS

The key aspects of pharmacotherapy include blood pressure management, blockade of the renin-angiotensin system, minimization of proteinuria, and avoidance of nephrotoxins.

The use of multiple antihypertensive drugs is often necessary to reach the blood pressure goal. Therefore, the primary care physician should be aware of the classes of drugs that may be of benefit beyond their antihypertensive effects.

IS AN ACE INHIBITOR OR ARB INDICATED?

Blockade of the renin-angiotensin system with an ACE inhibitor or ARB is generally desirable in a patient with chronic kidney disease attributed to diabetes or hypertension. Furthermore, an ACE inhibitor or ARB is indicated in diabetic patients with microalbuminuria or overt nephropathy (dipstick-positive proteinuria), regardless of the GFR or blood pressure.

A rise in creatinine of ≤ 30% on an ACE inhibitor is generally acceptable

TABLE 4

Myths and facts about ACE inhibitors

Myth:	ACE inhibitors should be avoided in chronic kidney disease
Fact:	ACE inhibitors are renoprotective in both diabetic and nondiabetic kidney diseases, mild as well as advanced
Myth:	ACE inhibitors are ineffective in African American patients
Fact:	Although not potent antihypertensives as monotherapy, ACE inhibitors can be effective as part of an overall antihypertensive treatment plan, and are renoprotective beyond their effects on blood pressure
Myth:	ACE inhibitors should be discontinued if any rise in creatinine occurs after initiation
Fact:	A rise in serum creatinine of up to 30% is acceptable
Myth:	ACE inhibitors should be stopped if any hyperkalemia develops
Fact:	Mild hyperkalemia can often be remedied by a low-potassium diet and discontinuation of drugs that decrease potassium excretion
Myth:	ACE inhibitors obviate the need to test and monitor for proteinuria or microalbuminuria
Fact:	Proteinuria and microalbuminuria are modifiable risk factors for renal failure; monitoring is an essential feature of preventive nephrology

These drugs have several desirable effects, including lowering systemic blood pressure, intraglomerular pressure, and proteinuria.

Despite considerable evidence that ACE inhibitors are beneficial in diabetic nephropathy and in nondiabetic renal diseases, these drugs are underused in chronic kidney disease in general. Hsu et al[16] found that only 27% to 38% of such patients in one health care system received ACE inhibitors, with the lower rates in patients with more advanced disease.

Don't stop the ACE inhibitor unnecessarily

Given the ample evidence of the benefit of this class of drugs, one should not stop an ACE inhibitor unless the patient truly cannot tolerate it (ie, develops cough, angioedema, or another allergic response) or develops moderate or severe hyperkalemia or acute renal insufficiency. The latter two situations call for clinical judgement and may result in unnecessarily stopping the drug for "soft" reasons.

Mild hyperkalemia (potassium < 5.6 mEq/L) can often be remedied by:

- Stopping potassium supplements, potassium-sparing diuretics, dietary salt substitutes, and nonsteroidal anti-inflammatory drugs (NSAIDs)
- Giving diuretics as appropriate, in particular twice-daily loop diuretics to promote potassium excretion
- Giving specific verbal and written advice on lowering dietary potassium.

A modest rise in creatinine on an ACE inhibitor may be good. A rise in serum creatinine of up to 30% within 1 to 2 weeks of starting an ACE inhibitor is generally acceptable, provided that it does not rise further on continued monitoring.

This increase may even be a good thing. Bakris and Weir[17] reviewed 12 clinical trials averaging 3 years of follow-up and found that an acute increase in serum creatinine of up to 30% was strongly associated with long-term preservation of renal function.

If the serum creatinine concentration rises by more than 30%, however, one should stop the ACE inhibitor and consider whether the patient has renal artery stenosis or another high-renin state such as hypovolemia or uncompensated heart failure. If such a condition is present and can be corrected (eg, hypovolemia treated by volume repletion), then it may be worthwhile to consider a second trial of an ACE inhibitor.

Considering the key role that ACE inhibitors play in preventive nephrology (and primary care medicine in general), their use should be based on fact rather than myths or misconceptions (TABLE 4).

When to consider an ARB

An ARB is indicated for patients who cannot tolerate ACE inhibitors. In general, neither cough nor angioedema should occur with an ARB; however, rare cases of angioedema have been reported.[18] Both irbesartan[19] and losartan[20] have been shown to slow progression in the nephropathy of type 2 diabetes.

Therefore, for the nephropathy of type 2 diabetes specifically, an ARB can be considered first-line therapy.[21] However, the merits of an ACE inhibitor as first-line therapy can also be argued, eg, on the basis of a more firmly established cardiovascular benefit.

The physiologic effects of ARBs are not identical to those of ACE inhibitors, but similar enough that the above discussion of the use of ACE inhibitors can generally be applied, for practical purposes, to ARBs.

Increase the ACE or ARB dose

If the blood pressure goal has been attained but proteinuria has not been substantially reduced, an increase in the dose of ACE inhibitor or ARB is in order.

Combine an ACE and an ARB?

Combining an ACE inhibitor with an ARB may hold promise. For instance, candesartan added to lisinopril resulted in a greater decrease in proteinuria and blood pressure than did either drug alone.[22] The long-term effects of this combination in the treatment of chronic kidney disease remain to be seen.

Add a calcium channel blocker?

The **nondihydropyridine calcium channel blockers** diltiazem and verapamil have antiproteinuric effects, and the combination of verapamil and the ACE inhibitor trandolapril has been shown to reduce proteinuria more than either drug alone.[23] Their antiproteinuric and potent antihypertensive effects make diltiazem and verapamil key components in treating chronic kidney disease.

The effects of **dihydropyridine calcium channel blockers** (nifedipine, amlodipine, felodipine, isradipine, nicardipine, nisoldipine) are less clear, but they seemed to worsen proteinuria in several studies, at least when used without an ACE inhibitor. For example, the amlodipine arm of the African American Study of Kidney Diseases was terminated after patients randomized to this drug experienced more proteinuria and a more rapid decline in renal function than did those receiving either metoprolol or ramipril.[24]

Not all trials demonstrated these undesirable renal effects of dihydropyridine calcium channel blockers, and these drugs can play an important role. While we await more clarity on this controversial issue, it is important to at least screen and monitor for proteinuria in patients with chronic kidney disease receiving these drugs.

PROTEINURIA MAY BE A CLUE TO AN UNDERLYING DISORDER

While minimizing proteinuria is an important treatment goal for patients with diabetes or hypertension, we should remember that proteinuria may be a clue to an occult renal or systemic disorder. For example:

- Monoclonal protein analysis of urine and blood may be indicated to investigate suspected multiple myeloma or amyloidosis.
- Hematuria, cellular casts, or other abnormalities in the urine sediment should prompt a referral to a nephrologist, as they suggest a condition such as glomerulonephritis, which may require more specific treatment.
- Heavy proteinuria in a diabetic patient without other microvascular disease (eg, retinopathy, neuropathy) may not be due to diabetic nephropathy, and early subspecialty referral may again be indicated.

BE ALERT FOR NEPHROTOXINS

In an office practice, the most important nephrotoxins are the **NSAIDs**, which have been associated with both acute and chronic kidney disease. Although definitive evidence of the risk of chronic NSAID use in mild chronic kidney disease is lacking, the primary care physician would do well to follow widely held expert opinion and avoid regular use of these drugs, except for aspirin in low doses.

It may be wise to avoid NSAIDs in chronic kidney disease

While we await further study about the renal effects of cyclo-oxygenase 2 (COX-2) inhibitors, it is best not to assume that these drugs are safe in this regard. Traditional NSAIDs and selective COX-2 inhibitors have been found to have essentially the same acute hemodynamic and renal effects, and use of drugs from either class can lead to sodium retention, hyperkalemia, edema, and increased blood pressure.[25] Both classes have been found in some cases to precipitate acute renal failure in chronic kidney disease.

OTHER KEY RENOPROTECTIVE STRATEGIES

Tight glycemic control for diabetic patients and **stopping cigarette smoking** are critically important in chronic kidney disease.

The bulk of the evidence regarding the renal benefit of intensive blood control is in regard to prevention[5]; however, tight control is the goal at all stages of kidney disease. Cigarette smoking has been associated with a faster decline in renal function in patients with essential hypertension[26] and diabetes, even with ACE inhibition.[27]

While pursuing these goals is standard in a primary care practice, educating the patient with kidney disease regarding the renal benefits involved may be a helpful motivating factor. The reader is referred to a comprehensive review of renoprotective strategies, including a detailed approach to controlling blood pressure[28]; described above are the essentials that the busy primary care doctor must address in patients at risk who have mild disease.

MONITORING AND REFERRAL

The National Kidney Foundation staging system can help guide the primary care physician on when to refer the patient to a nephrologist.

Patients in stage 1, 2, or 3 can usually be managed by a primary care physician.

However, patients in stage 3 (GFR 30–59 mL/minute) should be assessed for anemia, nutritional status, bone metabolism, and functioning and well-being.

Patients with stage 4 or stage 5 disease will benefit from timely referral to a nephrologist to maximize renoprotective strategies, to address the expected cormorbidities such as anemia, bone disease, malnutrition, and left ventricular hypertrophy, and to prepare for dialysis or transplantation.

REFERENCES

1. **Levey AS, Coresh J, Bolton K, et al.** K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002; 39(suppl 2):S1–S246.
2. **US Renal Data System.** USRDS 2000 annual data report. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2000.
3. **Jones CA, McQuillan GM, Kusek JW, et al.** Serum creatinine levels in the US population: third National Health and Nutrition Examination Survey [erratum appears in Am J Kidney Dis 2000; 35:178]. Am J Kidney Dis 1998; 32:992–999.
4. **Perry HM, Miller JP, Fornoff JR, et al.** Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension 1995; 25:587–594.
5. **UK Prospective Diabetes Study (UKPDS) Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352:837–853.
6. **Jafar TH, Stark PC, Schmid CH, et al.** Proteinuria as a modifiable risk factor for the progression of non-diabetic renal disease. Kidney Int 2001; 60:1131–1140.
7. **Keane WF.** Proteinuria: its clinical importance and role in progressive renal disease. Am J Kidney Dis 2000; 35:S97–S105.
8. **Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D.** A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999; 130:461–470.
9. **Cockroft DW, Gault MH.** Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16:31–41.
10. **Ruggenenti P, Perna A, Mosconi L, Pisoni R, Remuzzi G.** Urinary protein excretion rate is the best independent predictor of ESRF in non-diabetic proteinuric chronic nephropathies. "Gruppo Italiano di Studi Epidemiologici in Nefrologia" (GISEN). Kidney Int 1998; 53:1209–1216.
11. **Keane WF, Eknoyan G.** Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation. Am J Kidney Dis 1999; 33:1004–1010.
12. **Hebert LA, Spetie DN, Keane WF.** The urgent call of albuminuria/proteinuria. Postgrad Med 2001; 110:79–96.
13. **Bigazzi R, Bianchi S, Baldari D, Campese VM.** Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. J Hyperten 1998; 16:1325–1333.
14. **Heeg JE, de Jong PE, van der Hem GK, de Zeeuw D.** Efficacy and variability of the antiproteinuric effect of ACE inhibition by lisinopril. Kidney Int 1989; 36:272–279.
15. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. Arch Intern Med 1997; 157:2413–2446.
16. **Hsu C, Bates DW, Kuperman GJ, Curhan GC.** Blood pressure and angiotensin converting enzyme inhibitor use in hypertensive patients with chronic renal insufficiency. Am J Hypertens 2001; 14: 1219–1225.
17. **Bakris GL, Weir MR.** Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000; 160:685–693.
18. **Cha YJ, Pearson VE.** Losartan-induced angioedema. Ann Pharmacol 1999; 33:936–938.
19. **Lewis EJ.** Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001; 345:861–869.
20. **Brenner BM.** Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001; 345:851–860.
21. **American Diabetes Association Position Statement.** Diabetes Care 2002; 25:S85–S89.
22. **Mogensen CE, Neldam S, Tikkanen I, et al.** Randomised controlled trial of dual blockade of renin-angiotensin system in patients with hypertension, microalbuminuria, and non-insulin dependent diabetes: the candesartan and lisinopril microalbuminuria (CALM) study. BMJ 2000; 321:1440–1444.
23. **Bakris GL, Weir MR, DeQuattro V, McMahon FG.** Effects of an ACE inhibitor/calcium antagonist combination on proteinuria in diabetic nephropathy. Kidney Int 1998; 54:1283–1289.
24. **Agodoa LY, Appel L, Bakris GL, et al.** Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 2001; 285:2719–2728.
25. **Brater DC.** Renal effects of COX-2-selective inhibitors. Am J Nephrol 2001; 21:1–15.
26. **Regalado M.** Cigarette smoking is associated with augmented progression of renal insufficiency in severe essential hypertension. Am J Kidney Dis 2000; 35:687–694.
27. **Chuahirun T, Wesson DE.** Cigarette smoking predicts faster progression of established diabetic nephropathy despite ACE inhibition. Am J Kidney Dis 2002; 39:376–382.
28. **Hebert LA, Wilmer WA, Falkenhain ME, Ladson-Wofford SE, Nahman NS Jr, Rovin BH.** Renoprotection: one or many therapies? Kidney Int 2001; 59:1211–1226.

ADDRESS: Christopher J. Hebert, MD, Louis Stokes Cleveland VA Medical Center, 10701 East Boulevard, Cleveland, OH 44106; e-mail Christopher.Hebert@med.va.gov.

institution of interventional measures that have been shown to be effective in reducing proteinuria, retarding the progression of kidney disease, and improving cardiovascular mortality and morbidity, with the consequent improvement of outcomes for all individuals at increased risk.

Sir Robert Hutchison (1871–1960) must have had a premonition of things to come, when at the turn of the past century he noted that; the ghosts of dead patients that haunt us do not ask why we did not employ the latest fad of clinical investigation. They ask us, why did you not test my urine?

REFERENCES

1. **Keane WF, Eknoyan G.** Proteinuria, albuminuria, risk, assessment, detection and elimination (PARADE). A position paper of the National Kidney Foundation. Am J Kidney Dis 1999; 33:1004–1010.
2. **Grimm RH Jr, Sandsen KH, Kasiske B, Keane WM, Wahi M.** Proteinuria is a risk factor for mortality over 10 years of follow up. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Kidney Int 1997; 63(suppl 63):S10–S14.
3. **Peterson JC, Adler S, Burkart JM, et al.** Blood pressure control, proteinuria and the progression of renal disease. The Modification of Diet in Renal Disease Study. Ann Intern Med 1995; 123:754–762.
4. **Mutner P, He J, Hamm L, Loria C, Whelton P.** Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 2002; 13:745–753.
5. **Gerstein HC, Mann JF, Yi Q, et al.** Albuminuria and risk of cardiovascular events, death and heart failure in diabetic and nondiabetic individuals. JAMA 2001; 286:421–426.
6. **SoRelle R.** Increases in urinary albumin excretion predict risk of death from all causes as well as those from cardiovascular disease. Circulation 2002; 106:e9037–e9038.
7. **Leoncini G, Sacchi G, Viazzi F, et al.** Microalbuminuria identifies overall cardiovascular risk in essential hypertension. J Hypertens 2002; 20:1315–1321.
8. **Hillege HL, Fidler V, Diercks GF, et al.** Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in the general population. Circulation 2002; 106:1777–1782.
9. **Mann JFE, Gerstein HC, Pogue J, Bosch J, Yusuf S, for the HOPE Investigators.** Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. Ann Intern Med 2001; 134:629–636.
10. **Keane WF.** Proteinuria: Its clinical importance and role in progressive renal disease. Am J Kidney Dis 2000; 35:(suppl 1):S97–S105.
11. **Kashif W, Siddiqi N, Dincer AP, Dincer HE, Hirsch S.** Proteinuria: How to evaluate an important finding. Cleve Clin J Med 2003; 70:535–547.
12. **Schwab SL, Christensen RL, Dougherty K, Klahr S.** Quantification of proteinuria by the use of protein-to-creatinine ratios in single urine samples. Arch Intern Med 1987; 147:943–944.
13. **Chitalia VC, Kothari J, Wells EJ, et al.** Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine protein-creatinine ratio. Clin Nephrol 2001; 55:436–447.
14. **National Kidney Foundation.** K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: evaluation, classification and stratification. Am J Kidney Dis 2002; 39(suppl 1):S25–S27.

ADDRESS: Garabed Eknoyan, MD, Department of Medicine, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030; e-mail geknoyan@bcm.tmc.edu.

CORRECTIONS

Osteoporosis in men

(MARCH 2003)

"Osteoporosis in men: Suspect secondary disease first," by Angelo Licata, MD, PhD (Cleve Clin J Med 2003; 70:247–254) contained a typographic error. On page 251 the T-score range for osteopenia was listed as between –1.5 and –2.5. The World Health Organization criteria specify –1.0 to –2.5. We would like to thank Dr. Stefan Monev, of Oshkosh, Wis, for pointing this out.

Preventing kidney failure

(APRIL 2003)

TABLE 2 in "Preventing kidney failure: Primary care physicians must intervene earlier" by Christopher J. Hebert, MD (Cleve Clin J Med 2003; 70:337–344) contained a typographic error. The exponent of the serum albumin concentration should be positive, not negative. The corrected table is shown at right. We would like to thank Dr. Robert Misson, of San Luis Obispo, Cal, for pointing this out.

TABLE 2

Three formulas for calculating the glomerular filtration rate (GFR)

MDRD formula (most accurate – calculator at www.kdoqi.org)

$$GFR = 170 \times \text{serum creatinine concentration}^{-0.999} \times \text{age}^{-0.176} \times 0.762 \text{ (if female)} \times 1.18 \text{ (if race is black)} \times \text{blood urea nitrogen concentration}^{-0.17} \times \text{serum albumin concentration}^{0.318}$$

24-hour creatinine clearance
(intermediate accuracy, least convenient)

$$GFR = \frac{\text{urine creatinine concentration} \times \text{volume in mL}}{\text{serum creatinine concentration} \times \text{time in minutes}}$$

Cockroft-Gault formula (least accurate, most convenient)

$$GFR = \frac{(140 - \text{age}) \times \text{weight in kg} \times (0.85 \text{ if female})}{72 \times \text{serum creatinine concentration}}$$