Chronic Kidney Disease: Prevention and Treatment of Common Complications

CATHERINE S. SNIVELY, M.D., and CECILIA GUTIERREZ, M.D.
University of California, San Diego, School of Medicine, La Jolla, California

Chronic kidney disease is a progressive condition that results in significant morbidity and mortality. Because of the important role the kidneys play in maintaining homeostasis, chronic kidney disease can affect almost every body system. Early recognition and intervention are essential to slowing disease progression, maintaining quality of life, and improving outcomes. Family physicians have the opportunity to screen at-risk patients, identify affected patients, and ameliorate the impact of chronic kidney disease by initiating early therapy and monitoring disease progression. Aggressive blood pressure control, with a goal of 130/80 mm Hg or less, is recommended in patients with chronic kidney disease. Angiotensin-converting enzyme inhibitors and angiotensin-II receptor antagonists are most effective because of their unique ability to decrease proteinuria. Hyperglycemia should be treated; the goal is an A1C concentration below 7 percent. In patients with dyslipidemia, statin therapy is appropriate to reduce the risk of cardiovascular disease. Anemia should be treated, with a target hemoglobin concentration of 11 to 12 g per dL (110 to 120 g per L). Hyperparathyroid disease requires dietary phosphate restrictions, antacid use, and vitamin D supplementation; if medical therapy fails, referral for surgery is necessary. Counseling on adequate nutrition should be provided, and smoking cessation must be encouraged at each office visit. (Am Fam Physician 2004;70:1921-8,1929-30. Copyright© 2004 American Academy of Family Physicians.)

▶**Patient information:** A handout on chronic kidney disease, written by the authors of this article, is provided on page 1929.

See page 1845 for definitions of strength-of-recommendation levels.

ACF This article exemplifies the AAFP 2004 Annual Clinical Focus on caring for America's aging population.

The National Kidney Foundation (NKF)[1] defines chronic kidney disease as kidney damage or a glomerular filtration rate (GFR) of less than 60 mL per minute per 1.73 m^2 (body surface area) for three months or more.[1] This GFR rate corresponds with a serum creatinine concentration higher than 1.5 mg per dL (132.6 μmol per L) in men and higher than 1.3 mg per dL (114.9 μmol per L) in women.[2,3] Chronic kidney disease also can be defined by the presence of urinary albumin in an excretion rate higher than 300 mg per 24 hours or in a ratio of more than 200 mg of albumin to 1 g of creatinine[3] *(Table 1)*.[1,4,5]

Chronic kidney disease currently affects as many as 20 million Americans.[3] The incidence and prevalence of the disease have doubled in the past decade, most likely because improved treatments for hypertension, diabetes mellitus, and coronary disease have increased longevity in affected patients and, therefore, their likelihood of developing chronic kidney disease. Estimated medical and other economic costs of chronic kidney disease are expected to approach $28 billion annually by 2010, with an additional $90 billion in annual costs related to associated increased cardiovascular disease, infections, and hospitalizations.[3]

Causes of chronic kidney disease include diabetes mellitus, hypertension, ischemia, infection, obstruction, toxins, and autoimmune and infiltrative diseases. Although it is important to identify the cause(s) of chronic kidney disease so that specific therapy can be instituted, the disease often progresses despite appropriate treatment. As kidney function deteriorates, patients develop complications related to fluid overload, electrolyte and acid-base imbalances, and the build-up of nitrogenous waste. To survive, some patients eventually need hemodialysis or kidney transplantation.

This article reviews the current recommendations and therapeutic strategies for preventing or delaying the progression of chronic kidney disease and the development of complications such as hypertension, hyperglycemia, hyperlipidemia, anemia, and

TABLE 1
Definitions of Proteinuria and Albuminuria

Concentration measured	*Urine collection method*	*Normal value*	*Microalbuminuria*	*Albuminuria or clinical proteinuria*
Total protein	24-hour excretion (varies with method)	< 300 mg per 24 hours	—	> 300 mg per 24 hours
	Spot urine dipstick	< 30 mg per dL	—	> 30 mg per dL
	Spot urine protein-to-creatinine ratio (varies with method)	< 200 mg of protein to 1 g of creatinine	—	> 200 mg of protein to 1 g of creatinine
Albumin	24-hour urinary excretion	< 30 mg per 24 hours	30 to 300 mg per 24 hours	> 300 mg per 24 hours
	Spot urine albumin-specific dipstick	< 3 mg per dL	> 3 mg per dL	—
	Spot urine albumin-to-creatinine ratio (varies by sex*)	Men: < 17 mg of albumin to 1 g of creatinine Women: < 25 mg of albumin to 1 g of creatinine	Men: 17 to 250 mg of albumin to 1 g of creatinine Women: 25 to 355 mg of albumin to 1 g of creatinine	Men: > 250 mg of albumin to 1 g of creatinine Women: > 355 mg of albumin to 1 g of creatinine

**—Sex-specific cutoff values are from a single study.[4] Use of the same cutoff value for men and women leads to higher prevalence rates in women than in men. Current recommendations from the American Diabetes Association[5] define cutoff values for the spot urine albumin-to-creatinine ratio for microalbuminuria as 30 mg of albumin to 1 g of creatinine and the spot urine albumin-to-creatinine ratio for albuminuria as 300 mg of albumin to 1 g of creatinine without regard to sex.*

Adapted with permission from National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 suppl 1):S51.

renal osteodystrophy. Recommendations for nutrition and smoking cessation also are discussed.

CLASSIFICATION OF SEVERITY AND MONITORING OF DISEASE PROGRESSION

The GFR is used to assess the degree of kidney-function impairment and to monitor disease progression and treatment response. GFR is a measure of the overall filtration rate of all nephrons. In persons 30 years or younger, the normal GFR is approximately 125 mL per minute per 1.73 m^2; after the age of 30 years, GFR declines by 1 mL per minute per 1.73 m^2 per year.

Estimation of the GFR no longer requires a 24-hour urine collection for creatinine clearance but can be accomplished with similar accuracy using a mathematic formula.[1] The most commonly used formulas for estimating GFR in patients with stable chronic kidney disease are the Modification of Diet in Renal Disease (MDRD) equation and the Cockcroft-Gault equation *(Table 2)*.[6-8]

Proteinuria is another marker of kidney injury. It is measured in a timed (overnight or 24-hour) urine collection or in an untimed (spot) urine sample by calculating the ratio of protein or albumin to creatinine *(Table 1)*.[1,4,5]

The NKF Kidney Disease Outcome Quality Initiative (K/DOQI) stratifies chronic kidney disease into five stages based on the GFR and metabolic consequences *(Table 3)*.[1] The NKF suggests actions to slow disease progression.[1]

Table 2
Equations for Predicting GFR in Patients with Stable Chronic Kidney Disease*

Abbreviated MDRD study equation†:

$$\text{GFR (mL per minute per 1.73 m}^2\text{)} = 186 \times (S_{Cr})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$$

Cockcroft-Gault equation:

$$C_{Cr}\ (\text{mL per minute}) = \frac{(140 - \text{age}) \times \text{weight}}{72 \times S_{Cr}} \times (0.85 \text{ if female})$$

GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; S_{Cr} = serum creatinine concentration; C_{Cr} = creatinine clearance.

**—For each equation, S_{Cr} is in mg per dL, age is in years, and weight is in kg.*
†—The MDRD study equation is available in computer programs that calculate the result when patient data are entered.

Information from references 6 through 8.

HYPERTENSION

Hypertension is a frequent cause of chronic kidney disease. Systemic hypertension causes direct damage to small blood vessels in the nephron. The kidneys lose their ability to autoregulate glomerular filtration flow and pressure, with resultant hyperfiltration manifesting as albuminuria and proteinuria. When the proximal convoluted tubule reabsorbs the excess protein, secretion of vasoactive substances further damages the glomerular-tubular apparatus.[9] Nephron damage activates the renin-angiotensin-aldosterone system, resulting in increased sympathetic tone and fluid overload, which compound the progression of hypertension and nephron loss.[10]

Several trials[11-13] have demonstrated the benefit of strict blood pressure control in slowing the progression of kidney disease. Thus, the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a target blood pressure of less than 130/80 mm Hg in patients with chronic kidney disease.[2]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists preferentially lower intraglomerular pressure and reduce proteinuria. Ample evidence shows that these agents are more effective than other antihypertensive drugs in preventing the progression of kidney disease.[11,12,14-19]

The JNC-7 guidelines recommend a target blood pressure of less than 130/80 mm Hg in patients with chronic kidney disease .

The Ramipril Efficacy in Nephropathy study[15] found a significantly higher GFR and a lower rate of GFR decline in patients without diabetes who received the ACE inhibitor ramipril than in similar patients who were given placebo.

Angiotensin-II receptor antagonists have been shown to reduce the occurrence of kidney failure. Efficacy may be increased when

TABLE 3
Stages of Chronic Kidney Disease

Stage	*Description*	*GFR (mL per minute per 1.73 m²)*	*Metabolic consequences*
—	At increased risk	Higher than 60 (with risk factors for chronic kidney disease)	—
1	Kidney damage (early) with normal or elevated GFR	90 or higher	—
2	Kidney damage with mildly decreased GFR (early renal insufficiency)	60 to 89*	Parathyroid hormone level begins to rise (GFR of 60 to 80).
3	Moderately decreased GFR (moderate kidney failure)	30 to 59	Calcium absorption decreases (GFR below 50). Lipoprotein activity declines. Malnutrition develops. There is onset of left ventricular hypertrophy and/or anemia (erythropoietin deficiency).
4	Severely decreased GFR (pre–end-stage kidney disease)	15 to 29	Triglyceride concentration begins to rise. Hyperphosphatemia or metabolic acidosis develops. There is a tendency toward hyperkalemia.
5	Kidney failure (end-stage kidney disease [uremia])	< 15 (or dialysis)	Azotemia develops.

GFR = glomerular filtration rate.

**—May be normal for age.*

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these agents are given in combination with ACE inhibitors. In one study,[20] combination therapy with candesartan (angiotensin-II receptor antagonist) and lisinopril (ACE inhibitor) was more effective than treatment with either drug alone in reducing blood pressure and microalbuminuria in patients with type 2 diabetes, hypertension, and microalbuminuria.

When ACE-inhibitor therapy is started, some patients with chronic kidney disease may have an initial decrease in GFR (usually less than 10 mL per minute per 1.73 m^2), a mild increase in the serum creatinine concentration (less than 20 percent of the baseline value), and a mild increase in the potassium level (usually less than 0.5 mmol per L).[21] Therefore, serum creatinine and potassium levels should be monitored one to two weeks after the initiation of therapy with an ACE inhibitor.

The American Diabetes Association recommends glycemic control in patients with diabetes mellitus, with the goal being an A1C concentration below 7 percent.

DIABETES MELLITUS

Diabetes mellitus is the most common cause of chronic kidney disease.[22] Hyperglycemia is an independent risk factor for nephropathy.[23] The pathophysiology of diabetic nephropathy is complex and most likely involves both hemodynamic and glucose-dependent factors, including the accumulation of advanced glycated products, endothelial dysfunction, and loss of intraglomerular blood pressure regulation.[24] Studies have shown that the A1C level correlates with loss of renal function and that glycemic control reduces the progression of kidney disease.[25,26]

To prevent progression of nephropathy in patients with diabetes mellitus, the American Diabetes Association (ADA)[27] recommends glycemic control, with the goal being an A1C concentration below 7 percent. The ADA also recommends yearly screening for microalbuminuria and blood pressure control with an ACE inhibitor or angiotensin-II receptor antagonist.

DYSLIPIDEMIA

Dyslipidemia is a primary risk factor for cardiovascular disease and a common complication of progressive kidney disease. Most patients with chronic kidney disease have an abnormal lipid panel that increases their risk for atherogenesis. Dyslipidemia contributes to cardiovascular mortality, which is 10 to 20 times higher in dialysis patients than in the normal population even after adjustments are made for age, sex, and diabetes mellitus.[28,29]

The most noticeable lipid abnormality in chronic kidney disease is an elevated triglyceride level, possibly because of defective clearance.[30,31] Patients with chronic kidney disease also have an elevated ratio of low-density lipoprotein (LDL) cholesterol to high-density lipoprotein (HDL) cholesterol. LDL cholesterols, including lipoprotein(a), are pro-atherogenic, and levels are slightly elevated in patients with chronic kidney disease. Levels of oxidized LDL cholesterol also are elevated; these cholesterols activate pro-inflammatory pathways, thereby promoting atherogenesis and endothelial dysfunction. HDL cholesterol levels are decreased, indicating loss of anti-atherogenic effect.

Although no large randomized controlled trials have studied the effects of lipid reduction on the progression of kidney disease, animal models suggest that dyslipidemia worsens kidney function. A recent meta-analysis[32] of 13 small studies showed that lipid reduction preserves GFR and reduces proteinuria. The most recent guidelines from the NKF K/DOQI[33] recommend treating dyslipidemia

The Authors

CATHERINE S. SNIVELY, M.D., is a family physician at Imperial Beach Community Health Center, San Diego. Dr. Snively received her medical degree from the George Washington University School of Medicine and Health Sciences, Washington, D.C., and completed a family medicine residency at the University of California, San Diego, School of Medicine, La Jolla.

CECILIA GUTIERREZ, M.D., is assistant clinical professor in the Department of Family and Preventive Medicine at the University of California, San Diego, School of Medicine, where she also is associate director of the family medicine residency program. Dr. Gutierrez graduated from the University of California, Irvine, College of Medicine and completed a family medicine residency at the University of California, San Diego, School of Medicine.

Address correspondence to Cecilia Gutierrez, M.D., Department of Family and Preventive Medicine, University of California, San Diego, School of Medicine, 9500 Gilman Dr., Mail Code 0807, La Jolla, CA 92093. Reprints are not available from the authors.

aggressively in patients with chronic kidney disease. The goals are an LDL cholesterol level below 100 mg per dL (2.60 mmol per L) and a triglyceride level below 200 mg per dL (2.26 mmol per L).[33]

Fibrates are known to decrease triglyceride levels, but they may increase the risk for rhabdomyolysis in patients with chronic kidney disease. Statins can lower cholesterol levels safely and effectively in these patients, although research has not yet shown that treatment decreases cardiovascular mortality.[34]

ANEMIA

The anemia of chronic renal disease is normocytic and normochromic. It occurs primarily because of lower production of erythropoietin by the decreased mass of functioning renal tubular cells.

Anemia results in fatigue, reduced exercise capacity, decreased cognition, and impaired immunity. Thus, it decreases quality of life. In addition, increased workload on the heart as a result of anemia can lead to left ventricular hypertrophy and maladaptive cardiomyopathy. These conditions increase the risk of death from heart failure or ischemic heart disease.[35]

Study results[36,37] have shown that correction of anemia can limit the progression of chronic kidney disease and possibly decrease mortality. The NKF K/DOQI guidelines[1] recommend a target hemoglobin concentration of 11 to 12 g per dL (110 to 120 g per L) in patients with chronic kidney disease. Patients with plasma ferritin concentrations below 100 ng per mL (100 mcg per L) should be given iron supplements.

Erythropoietin should be administered to predialysis patients who have anemia-dependent angina or severe anemia with a hemoglobin concentration below 10 g per dL (100 g per L).[38] Hypertension and an increased risk for thrombotic events are potential adverse effects of treatment. Therefore, patients receiving erythropoietin must be monitored closely.

RENAL OSTEODYSTROPHY

Changes in mineral metabolism and bone structure begin early in chronic kidney disease. These changes include osteitis fibrosa cystica (because of secondary hyperparathyroidism); less commonly, osteomalacia (defective mineralization); and adynamic bone disease (absence of cellular activity).[39] Osteitis fibrosa cystica, the predominant bone defect, is characterized by an increase in bone turnover that leads to decreased cortical bone and impaired bone strength. Bone disease can result in pain and an increased risk of fracture.

Parathyroid hormone levels begin to rise when creatinine clearance falls below 60 mL per minute (1 mL per second).[1] The development of hyperparathyroidism may be prevented by restricting dietary phosphate intake (e.g., colas, nuts, peas, beans, dairy products), using a calcium-based phosphate binder (antacid) with meals, and administering vitamin D (Rocaltrol) to suppress parathyroid hormone secretion.[39] Vitamin D supplementation is safe and effective for lowering parathyroid hormone secretion in patients with elevated parathyroid hormone levels or hypocalcemia despite adequate correction of hyperphosphatemia.[40]

Even with appropriate medical therapy, some patients continue to have refractory hyperparathyroidism because of parathyroid gland hyperplasia. These patients should be referred for surgical treatment.

NUTRITION

Patients with chronic kidney disease are at risk for malnutrition and hypoalbuminemia. Both of these conditions are associated with poor outcomes in patients who are beginning dialysis.[41]

The effect of dietary protein restriction on kidney disease is the subject of debate. Some studies suggest that dietary protein restriction slows the progression of kidney disease, particularly in patients with diabetes mellitus.[41] However, these studies were confounded by the benefits of ACE-inhibitor therapy on the rate of disease progression.

The MDRD study[42] attempted to determine a level of protein intake that might reduce the risk of kidney disease progression and also minimize the risk of malnutrition. The study evaluated three levels of dietary

Strength of Recommendation

Key clinical recommendations	Label	References
The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a target blood pressure of less than 130/80 mm Hg in patients with chronic kidney disease.	C	2
According to the evidence, ACE inhibitors are more effective than other antihypertensive drugs in preventing the progression of kidney disease in diabetic and nondiabetic patients.	A	12-15
Angiotensin-II receptor antagonists have been shown to reduce proteinuria and the occurrence of kidney failure.	A	17-21
To prevent progression of nephropathy in patients with diabetes mellitus, the American Diabetes Association recommends glycemic control, with the goal being an A1C concentration below 7 percent.	C	27
The most recent guidelines from the NKF K/DOQI recommend treating dyslipidemia aggressively in patients with chronic kidney disease. The goals are an LDL cholesterol level below 100 mg per dL (2.60 mmol per L) and a triglyceride level below 200 mg per dL (2.26 mmol per L).	C	33

ACE = angiotensin-converting enzyme; NKF K/DOQI = National Kidney Foundation Kidney Disease Outcome Quality Initiative; LDL = low-density lipoprotein.

protein intake and found that a very-low-protein diet (0.28 g per kg per day) slightly decreased the rate of progression of proteinuria compared with diets with higher protein intake (0.56 g per kg per day and 1.3 g per kg per day). The very-low-protein diet did not result in malnutrition, but it also did not decrease progression to kidney failure or death.

Current recommendations from the NKF K/DOQI based on evidence from animal studies suggest a protein intake of 0.8 to 1.0 g per kg per day and a daily caloric intake of 30 to 35 kcal per kg per day in patients with chronic kidney disease.[1] Patients with chronic kidney disease, particularly those requiring dialysis, need to be monitored closely every one to three months for serum albumin concentration and body weight so that appropriate interventions can be instituted to prevent malnutrition. Early referral to a nutritionist can help maintain optimal protein and caloric intake in these patients.

SMOKING CESSATION

Smoking is a strong risk factor for cardiovascular mortality in patients at risk for chronic kidney disease.[43] It also is strongly associated with the progression of nephropathy.[43] The results of one small study[44] showed that smoking cessation reduced the progression of kidney disease by 30 percent in patients with type 1 diabetes.

Smoking cessation should be strongly encouraged at each office visit. Patients should be offered nicotine-replacement therapies (e.g., patch, gum) and the antidepressant bupropion (Zyban).[45]

UREMIA

Despite optimal treatment, kidney function may continue to deteriorate. Ultimately, patients may develop uremia and kidney failure.[46] Symptoms of uremia include anorexia, nausea, vomiting, malaise, asterixis, muscle weakness, platelet dysfunction, pericarditis, mental status changes, seizures and, possibly, coma. These symptoms result from the accumulation of several toxins in addition to urea; thus, no strict correlation exists between clinical presentation and plasma blood urea nitrogen and creatinine levels.

Acute uremia or uremia resulting from progressive disease is an indication for immediate dialysis. Patients with kidney failure should be evaluated for kidney transplantation.

Members of various family practice departments develop articles for "Practical Therapeutics." This article is one in a series from the Department of Family and Preventive Medicine at the University of California, San Diego, Family Medicine Residency Program. Coordinator of the series is Tyson Ikeda, M.D.

The authors indicate that they do not have any conflicts of interest. Sources of funding: none reported.

The authors thank Roland Blantz, M.D., professor of nephrology, and William Norcross, M.D., professor of clinical medicine, University of California, San Diego, School of Medicine, for help in the preparation of the manuscript.

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