Annals of Internal Medicine®

In the Clinic®

Chronic Kidney Disease

Screening and Prevention

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Patient Information

Chronic kidney disease (CKD) affects more than 20 million Americans, and over 500 000 have end-stage renal disease (ESRD) (1–2). The most common causes of CKD are diabetes and hypertension. CKD is an independent risk factor for cardiovascular disease, cognitive dysfunction, hospitalization, and all-cause mortality. In older CKD patients, the risk for cardiovascular disease and all-cause mortality is often higher than the risk for progression to ESRD and depends on the level of kidney function, proteinuria, and age (3–5).

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CME Objective: To review current evidence for screening, and prevention, diagnosis, treatment, and practice improvement of chronic kidney disease.

Funding Source: American College of Physicians.

Disclosures: Drs. Drawz and Rahman, ACP Contributing Authors, have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-2715.

With the assistance of additional physician writers, ***Annals of Internal Medicine*** editors develop **In the Clinic** using resources of the American College of Physicians, including **ACP Smart Medicine** and **MKSAP** (Medical Knowledge and Self-Assessment Program).

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Other complications of CKD include metabolic abnormalities, such as anemia, secondary hyperparathyroidism, and electrolyte disturbances. The main goals of treatment include slowing the decline in kidney function, preventing cardiovascular disease, treating complications, and facilitating transition to renal replacement therapy when indicated. Management of these challenging patients is best accomplished through collaboration between primary care providers and nephrologists.

Screening and Prevention

Which patients are at increased risk for CKD?

The two most common causes of CKD in the United States are diabetes and hypertension (2). **Table 1** shows other risk factors for CKD (6–7).

Table 1. **Risk Factors for Chronic Kidney Disease**

Diabetes
Hypertension
Autoimmune diseases
Systemic infections
Urinary tract infections
Nephrolithiasis
Lower urinary tract obstruction
Hyperuricemia
Acute kidney injury
Family history of chronic kidney disease
Sociodemographic factors
Older age
Black race
Smoking
Heavy alcohol use
Obesity
Nonsteroidal anti-inflammatory drugs

Should clinicians screen patients for CKD?

Universal screening for CKD in adults is not recommended. In fact, the U.S. Preventive Services Task Force recommends against screening in asymptomatic individuals (8). However, individuals at increased risk for CKD should be screened, such as those older than 55 years and those with hypertension and diabetes (9).

How should patients be screened for CKD?

Screening should test for markers of kidney damage and estimate the glomerular filtration rate (GFR) (10). Therefore, it should include a serum creatinine measurement to estimate GFR, urinalysis to evaluate for leukocytes and red blood cells, and measurement of urine protein using either standard or albumin-specific dipsticks (6). Individuals who test positive for albumin or protein should have protein measured to calculate a protein-to-creatinine or albumin-to-creatinine ratio (**Table 2**) (6). Patients with type 2 diabetes should be screened for albuminuria in a spot urine sample at the time of diagnosis and then annually using >30 mg/g creatinine as the indicator for a positive test result (11).

Are preventive measures useful for patients at increased risk for CKD?

In patients with diabetes, good glycemic control reduces the risk for CKD, and hyperglycemia is associated with development and progression of diabetic nephropathy. Diabetic patients should use dietary interventions, oral hypoglycemic medications, and insulin as needed to maintain a hemoglobin (Hb) A_{1c} level of about 7% (12–14).

A total of 1375 participants from the DCCT (Diabetes Control and Complications Trial) was followed as part of the EDIC (Epidemiology of Diabetes Interventions and Complications) observational study. Over 22 years of follow-up,

Table 2. **Categories for Urine Albumin- and Protein-to-Creatinine Ratio***

Measure, mg/g	*Normal to Mildly Increased*	*Moderately Increased*	*Severely Increased*
Albumin-to-creatinine ratio	<30	30–300	>300
Protein-to-creatinine ratio	<150	150–500	>500

* *Adapted from reference 12.*

intensive diabetes therapy reduced the incidence of an estimated GFR <60 mL/min/1.73m^2 by 50% (95% CI, 18–69) (15).

In the U.K. Prospective Diabetes Study, 3867 patients with newly diagnosed type 2 diabetes were randomly assigned to conventional treatment with a goal fasting plasma glucose level <270 mg/dL (15 mmol/L) or intensive treatment with a goal fasting plasma glucose level <108 mg/dL (6 mmol/L). The mean HbA_{1c} level was 7.9% in the conventional-treatment group and 7.0% in the intensive-treatment group. Microalbuminuria developed in 27% of patients in the intensive-treatment group compared with 39% of patients in the conventional-treatment group (P = 0.033) (16).

Hypertension is the second most common cause of CKD in the United States and hastens decline in renal function regardless of the primary cause. Most patients with hypertension should maintain blood pressure <140/90 mm Hg by using lifestyle modification and antihypertensive drug therapy (17). However, although treating hypertension reduces the risk for cardiovascular events, reducing blood pressure does not reduce the risk for CKD.

Screening and Prevention... Patients older than 55 years and those with hypertension and diabetes should be screened for CKD by estimating GFR from serum creatinine measurement and urinalysis. Screening for proteinuria in patients with diabetes can be done by using the urine albumin- or protein-to-creatinine ratio. Maintaining strict glycemic control to prevent CKD in patients with diabetes is essential.

CLINICAL BOTTOM LINE

Diagnosis

What is the definition of CKD?

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) and the National Kidney Foundation (NKF) Kidney Disease Outcomes and Quality Initiative (K/DOQI) guidelines define CKD as kidney damage or a GFR <60 mL/min/1.73 m^2 for more than 3 months (6, 12). The guidelines define kidney damage as either functional abnormalities of the kidneys (such as proteinuria or albuminuria, or abnormalities of the urinary sediment, such as dysmorphic red cells) or structural abnormalities as noted on imaging studies (6, 12).

If the KDIGO definition is applied to data from the National Health and Nutrition Examination Survey, more than 20 million U.S. adults have CKD (1). From 1999 to 2009, the prevalence of this disorder increased by 20%–25% according to estimates from the U.S. Renal Data System (18).

How should clinicians estimate GFR and the stage of CKD?

The most common method for estimating GFR is the simplified

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Modification of Diet in Renal Disease equation

GFR in mL/min/1.73 m^2 = 186.3 × (serum creatinine in mg/dL)$^{-1.154}$ × age$^{-0.203}$ × (1.210 if black) × (0.742 if female)

Chronic Kidney Disease Epidemiology Collaboration equation

GFR = 141 × min(Scr/κ,1)$^{\alpha}$ × max(Scr/κ,1)$^{-1.209}$ × 0.993^{Age} × (1.018 if female) × (1.159 if black)

Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Modification of Diet in Renal Disease equation (see the Box) (19). A newer formula is the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (see the Box). This equation more precisely estimates GFR and more accurately categorizes risk for mortality and ESRD (20–21).

Estimating GFR allows a more accurate measure of renal function than serum creatinine alone, particularly in older patients (22). Clinicians should then classify the stage of CKD according to the patient's estimated GFR and urine albumin-to-creatinine ratio as shown in the **Figure** (12).

What clinical manifestations should clinicians look for when evaluating patients who may have CKD?

Mild-to-moderate CKD (estimated GFR >30 mL/min/1.73 m^2) is usually an asymptomatic disorder with no physical findings specific to decreased kidney function. However, a careful history and physical examination can reveal the cause of CKD, and the examination should focus on findings associated with diabetes and hypertension because they are by far the most common causes of CKD. Patients with long-standing, poorly controlled diabetes who have other diabetic complications, such as retinopathy and peripheral neuropathy, are likely to have diabetic nephropathy, especially if they have proteinuria. Similarly, patients with long-standing hypertension with hypertensive retinopathy and a family history of hypertension and CKD are likely to have hypertensive nephrosclerosis, especially if urinalysis reveals minimal proteinuria and no hematuria (23). It is worth noting that the presence of hypertension or diabetes does not rule out another cause of CKD, particularly since hypertension is a consequence of CKD. In addition, distinguishing between hypertensive and diabetic nephropathy is frequently difficult. However, a biopsy is usually not recommended because distinguishing between diabetes and hypertension as the underlying cause of CKD does not change management.

If hypertension and diabetes are not present, a careful history and physical examination may reveal other causes of CKD; for example, a history of heart failure or cirrhosis suggests decreased renal perfusion from decreased effective intravascular volume as well as renal injury from inflammation and activation of the sympathetic and renin-angiotensin-aldosterone systems (24–25). Infection with hepatitis B or C virus or HIV may cause CKD and proteinuria, so clinicians should ask all patients about intravenous drug use and high-risk sexual behavior. A family history of kidney disease may be a clue to the diagnosis of polycystic kidney disease, the Alport syndrome (glomerulonephritis, ESRD, and hearing loss), or medullary cystic kidney disease. Urinary frequency, hesitancy, incontinence, nocturia, dysuria, or hematuria may reflect underlying urinary tract disease, such as obstruction or infection (26–27). A rash, arthritis, mononeuropathy, or systemic symptoms suggests vasculitis or lupus. Clinicians should ask about recent diarrhea, bleeding, and dehydration because volume loss may decrease renal perfusion and cause acute kidney injury, which predisposes to CKD (28). Finally, a thorough medication history of prescription and over-the-counter drugs may reveal a medication that can cause CKD or require dose-adjustment because of loss of kidney function.

Physical examination should include measuring blood pressure and checking for orthostasis in

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Figure. **Stage of chronic kidney disease by GFR and albuminuria categories.**

GFR Categories (mL/min/1.73 m²) Stage, Description, and Range				Persistent Albuminuria Categories, Description and Range		
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g (<3 mg/mmol)	30-300 mg/g (3-30 mg/mmol)	>300 mg/g (>30 mg/mmol)
	1	Normal or high	≥90	1 if CKD	1	2
	2	Mildly decreased	60–89	1 if CKD	1	2
	3a	Mildly to moderately decreased	45–59	1	2	3
	3b	Moderately to severely decreased	30–44	2	3	3
	4	Severely decreased	15–29	3	3	4+
	5	Kidney failure	<15	4+	4+	4+

GFR and albuminuria categories inform the risk for progression. Green indicates low risk, yellow indicates moderately increased risk, orange indicates high risk, and red indicates very high risk. The numbers in each box are recommendations for the frequency of monitoring/year. GFR = glomerular filtration rate. From reference 12, with permission.

patients with recent fluid loss. The patient should also be evaluated for rashes and petechiae, and the fundus should be examined for diabetic retinopathy (microaneurysms, dot hemorrhages, and cotton wool spots) or hypertensive retinopathy (atrioventricular nicking, silver wiring, tortuosity, hemorrhages, exudates, and papilledema). The physician should evaluate the patient for heart failure by looking for pulmonary rales, jugular venous distention, an S3, and peripheral edema. A renal bruit suggests renal artery stenosis (29), and inflamed joints suggest vasculitis or autoimmune processes. Asterixis and encephalopathy can indicate uremia and the need for prompt initiation of dialysis (30).

What laboratory tests and imaging should be done?

GFR should be estimated in every CKD patient through measurement of serum creatinine levels by using one of the equations mentioned in the Box. Most laboratories routinely report estimated GFR. Serum electrolytes (sodium, potassium, chloride, and bicarbonate) should be measured along with a complete blood count; lipid profile; and urinalysis for specific gravity, pH, red blood cells, and leukocyte counts (19, 31). In patients with a GFR <60 mL/min/1.73 m^2, serum calcium, phosphorus, parathyroid hormone, and albumin levels should be measured. Renal ultrasonography should be done in all patients with CKD to look for hydronephrosis, cysts, and stones and to assess echogenicity, size, and symmetry of the kidneys (12). Finally, if suggested by the history, physical examination, and urinalysis, antinuclear antibodies should be measured to evaluate for lupus; serologic testing should be done to evaluate for hepatitis B and C virus and HIV; serum antineutrophil cytoplasmic antibodies should be measured to evaluate for vasculitis; and serum and urine protein immunoelectrophoresis should

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Table 3. **Classification of CKD Based on the Presence or Absence of Systemic Disease and the Kidney Location of Pathologic Findings***

Diseases	*Examples of Systemic Diseases Affecting the Kidney*	*Examples of Primary Kidney Diseases (Absence of Systemic Disease)*
Glomerular	Diabetes, systemic autoimmune diseases, systemic infections (bacterial endocarditis, hepatitis B and C, HIV), drugs, neoplasia (including amyloidosis)	Diffuse, focal, or crescentic proliferative glomerulonephritis; focal and segmental glomerulosclerosis; membranous nephropathy; minimal change disease
Tubulointerstitial	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary tract infections, stones, obstruction
Vascular	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital	Polycystic kidney disease, the Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies

* *Adapted from reference 12.*

be done to test for multiple myeloma.

Proteinuria is useful for diagnosing CKD and assessing prognosis because it is an independent predictor of the risk for both progression of renal disease and cardiovascular disease (32–33). Hematuria and other urinary sediment abnormalities can also help in the differential diagnosis of CKD; for example, dysmorphic red blood cells and especially red blood cell casts suggest active glomerular disease. Because patients with CKD are at high risk for cardiovascular disease (3–4), risk factors should be thoroughly assessed; such assessment includes a lipid profile. Finally, testing is needed for hyperkalemia, acidosis, hypocalcemia, and hyperphosphatemia, especially in stages 4 and 5 CKD.

How should clinicians classify CKD and construct a differential diagnosis?

In addition to classifying patients by GFR and albuminuria, clinicians should determine the cause of CKD based on the presence or absence of systemic disease and presumed location of kidney damage (glomerular, tubulointerstitial, vascular, or cystic) (**Table 3**) (12). For practical purposes, given the high prevalence of diabetes and hypertension in the United States, clinicians can classify patients with CKD into 1 of 3 broad categories: diabetic kidney disease; hypertensive kidney disease; and nonhypertensive, nondiabetic kidney disease (2).

When should clinicians consider consulting with a nephrologist for diagnosing patients with possible CKD?

A nephrology consultation should be obtained early in the course of the diagnostic evaluation in patients with persistent proteinuria (albumin-to-creatinine ratio ≥300 mg/g), the nephritic syndrome (hematuria, proteinuria, and hypertension), sustained hematuria (red blood cell casts or red blood cells >20/high-power field), no clear cause of CKD, or type 2 diabetes with proteinuria but no coexistent retinopathy or neuropathy (12). Patients whose kidney function declines relatively rapidly (>5 mL/min/1.73 m^2 per year) may also benefit from nephrology consultation. These patients may have a less common cause of CKD, such as membranous nephropathy or lupus nephritis. A kidney biopsy may be required for a definitive diagnosis, and immunosuppressive therapies may be helpful in these patients.

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Diagnosis... CKD is defined as kidney damage or a GFR <60 mL/min/1.73 m^2 for a period longer than 3 months. CKD should be classified based on levels of GFR and albuminuria. The first step in diagnosis is to determine whether a patient has diabetic nephropathy; hypertensive nephropathy; or nondiabetic, nonhypertensive kidney disease. The history and physical examination often point to a cause, but a definitive diagnosis requires various diagnostic tests, renal ultrasonography, and sometimes renal biopsy.

CLINICAL BOTTOM LINE

Treatment

What nondrug therapies should clinicians recommend?

Lifestyle and dietary modifications are effective for specific types of CKD. Clinicians should advise all patients with CKD to quit smoking; exercise for 30 minutes most days of the week; limit alcohol intake (1 drink/day for women, 2 drinks/day for men); maintain body mass index within the normal range (18.5–24.9 kg/m^2); and eat a diet high in fruit, vegetables, and whole grains (34–35). The DASH diet is recommended for patients with a GFR >60 mL/min/1.73 m^2 and high-normal blood pressure or stage 1 hypertension but not those with lower GFR (CKD stages 3 or 4) because it contains a higher-than-recommended amount of protein, potassium, and phosphorous (34). Although salt restriction in the general population is controversial, CKD patients with hypertension should restrict their dietary salt intake to <2.0 g/d (36). Most patients with CKD should avoid high-protein diets (>1.3 g/kg/day) (12). Finally, patients with stage 4 or 5 CKD should consider a low-protein diet (0.6 g/kg/day) under the guidance of a dietician specializing in renal disease (37–40).

Which drugs and other agents cause acute kidney injury in patients with CKD?

Patients with CKD are much more likely to have acute kidney injury from nephrotoxic agents than persons with normal renal function. Therefore, known nephrotoxic medications, such as aminoglycoside antibiotics, amphotericin B, nonsteroidal anti-inflammatory drugs (41), and radiocontrast agents, should be avoided. If radiocontrast agents are essential, intravenous sodium bicarbonate or 0.9% normal saline should be given before and after the procedure for patients at increased risk for contrast nephropathy (42–43). Given the low risk and potential for benefit, N-acetylcysteine before and after radiocontrast induction can be given to high-risk patients (44–45). Exposure to high doses of gadolinium contrast in patients with stage 4 or 5 CKD should also be avoided because of the risk for nephrogenic systemic fibrosis (46). Finally, although not necessarily a risk for renal injury, the dosing of several medications needs to be adjusted to avoid other adverse effects (47).

In a study of primary angioplasty, 119 patients were assigned to a double dose of N-acetylcysteine, 116 patients to standard-dose N-acetylcysteine, and 119 patients to placebo. All patients received intravenous fluids for 12 hours after the procedure at a rate of 1 mL/kg/h. Contrast medium–induced nephropathy, defined as an increase in the serum creatinine of 25% or more, was observed in 8% of patients in the double-dose group, 15% of pa-

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tients in the standard-dose group, and 33% of the patients in the placebo group (P < 0.001) (45).

In ACT (Acetylcysteine for Contrast-Induced Nephropathy Trial), 2308 patients undergoing angiography were randomly assigned to acetylcysteine 1200 mg or placebo twice daily for two doses before and two doses after the procedure. Contrast-induced acute kidney injury, defined as an increase in serum creatinine ≥25%, was observed in 12.7% of patients in the acetylcysteine group and 12.7% of patients in the control group (P = 0.97) (48).

What is the role of blood pressure management?

Patients with CKD are at high-risk for cardiovascular disease, and treatment of hypertension reduces this risk (34). Patients with CKD and hypertension should be treated to a goal blood pressure of <140/90 mm Hg (15, 36). In patients with significant proteinuria, some nephrologists treat to a goal blood pressure of <130/80 mm Hg, and KDIGO suggests a blood pressure target of <130/80 mm Hg for patients with a urine albumin-to-creatinine ratio of >30 mg/g (36).

The AASK (African American Study of Kidney Disease and Hypertension) enrolled 1094 African Americans with a GFR between 20 and 65 mL/min/1.73 m^2. Patients were randomly assigned to either a low target blood pressure of approximately 125/75 mm Hg or a usual target blood pressure of 140/90 mm Hg and treated for a median of 3.8 years. There was no difference in rate of GFR decline between the low and usual blood pressure target groups. At the conclusion of the trial, participants were enrolled in an observational study. In long-term follow up, the hazard ratio for the low blood pressure target compared with the usual blood pressure target was 0.91 (CI, 0.77–1.08) for progression of kidney disease (doubling of serum creatinine, ESRD, or death). Among participants with a urine protein–to–creatinine ratio >0.22, the low blood pressure target was associated with reduced risk for progression of kidney disease. However, more than two thirds of participants had a ratio ≤0.22, and there was no difference in kidney disease progression in this group (49–50).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) should be the preferred antihypertensive agents because they improve kidney outcomes in patients with CKD (17). The reduction in adverse renal outcomes with these drugs may be limited to patients with proteinuria that exceeds 0.5 g/day (51). Patients with CKD and hypertension often require combination therapy to achieve goal blood pressures. When combination therapy is used, diuretics are important because they reduce extracellular fluid volume, blood pressure, and risk for cardiovascular disease in CKD (4). They also potentiate the effects of ACE inhibitors, ARBs, and other antihypertensive agents. The choice of diuretic depends on the level of GFR: A thiazide-type diuretic should be used in patients with an estimated GFR ≥30 mL/min/1.73 m^2 and a loop diuretic, such as furosemide, when GFR is <30 mL/min/1.73 m^2.

When should clinicians prescribe ACE inhibitors versus ARBs?

ACE inhibitors and ARBs decrease the progression of diabetic nephropathy even in patients without hypertension (52–54). Although ACE inhibitors have mostly been studied in type 1 diabetes and ARBs in type 2 diabetes, it is reasonable to consider them equivalent for reducing risk for progression of diabetic nephropathy. ACE inhibitors or ARBs should be prescribed to CKD patients with either hypertension or diabetes who have urine albumin excretion >30 mg/day (55). In patients with nondiabetic proteinuria, ACE inhibitors or ARBs decrease proteinuria and reduce the risk for a doubling of serum creatinine or ESRD, regardless of underlying hypertension (51, 56). Combination ACE inhibitor–ARB therapy is not recommended in

patients with CKD due to increased risk for adverse renal events and hyperkalemia (57–58).

Patients treated with ACE inhibitors or ARBs need to be monitored closely for side effects, specifically hypotension, GFR decline, and hyperkalemia. Measure blood pressure, GFR, and potassium within 4 weeks of starting treatment or adjusting the dose if any of the following are present: systolic blood pressure less than 120 mm Hg or greater than 140 mm Hg; GFR less than 60 mL/min per 1.73 m^2; a decline in GFR greater than 15% in the last 2 months; or a potassium greater than 4.5 mEq/L. Otherwise, these variables should be checked within 12 weeks of initiating or altering the dose of ACE inhibitors or ARBs. In patients with CKD, GFR may transiently decline after an ACE inhibitor or ARB is started. It is usually safe to continue the medication if GFR decline is <30% from baseline over 4 months and serum potassium level is <5.5 mEq/L (34).

In a prospective trial of patients with diabetic nephropathy, 207 patients received captopril and 202 received placebo. Over a median follow-up of approximately 2.5 years, serum creatinine concentrations doubled in 25 patients in the captopril group, compared with 43 patients in the placebo group (P = 0.007). Captopril treatment reduced risk for the combined end point of death, dialysis, and transplantation by 50% (53).

IDNT (Irbesartan Diabetic Nephropathy Trial), was a randomized, double-blind, placebo-controlled study that compared irbesartan with amlodipine and irbesartan with placebo in hypertensive patients with type 2 diabetes. Compared with amlodipine, irbesartan reduced risk for a composite outcome of doubling serum creatinine levels, ESRD, and death by 23% (P = 0.02). Compared with placebo, irbesartan reduced risk for the composite outcome by 20% (P = 0.006); it also reduced proteinuria more than amlodipine and placebo (59).

What is the role of glycemic control in patients with diabetes and CKD?

Diabetes is the most common cause of ESRD in the United States (2). Poor glycemic control is associated with development and progression of diabetic nephropathy via alterations in tubuloglomerular feedback, abnormalities in polyol metabolism, and formation of advanced glycation end products. Therefore, patients with diabetes and CKD should maintain good glycemic control to reduce the incidence of proteinuria, progression of CKD, and possibly even reduce the incidence of ESRD (13). However, CKD increases the risk for hypoglycemia. Further, in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, more intense treatment was associated with increased all-cause mortality (61). Therefore, targeting an HbA_{1c} level <7% is no longer suggested; current CKD guidelines recommend a goal of about 7% (14). Finally, metformin should be avoided in CKD patients with a GFR <30 mL/min/1.73 m^2 (62–63).

The DCCT (Diabetes Control and Complications Trial) enrolled 1441 patients with type 1 diabetes who were randomly assigned to conventional treatment with 1 or 2 daily injections of insulin and daily monitoring of glucose, intensive therapy with 3 or more daily injections of insulin, or an external pump combined with self-monitoring of blood glucose levels at least 4 times/day. Average blood glucose level was 231 mg/dL (12.8 mmol/mL) with conventional treatment and 155 mg/dL (8.6 mmol/mL) with intensive treatment. In the primary intervention group (consisting of patients without microalbuminuria, defined as >40 mg/day), intensive treatment reduced the incidence of microalbuminuria by 34% (P = 0.04). In the secondary intervention group (consisting of patients with mild-to-moderate retinopathy and ≤200 mg albuminuria/day), intensive treatment reduced the incidence of albuminuria (defined as ≥300 mg/day) by 56% (P = 0.01) (64). At the conclusion of the DCCT, 1375 participants were followed as part of the EDIC (Epidemiology of Diabetes Interventions and Complications) study. Over a median follow-up of 22 years, intensive therapy was associated with a 50% reduction (CI,18–69) in

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the incidence of impaired estimated GFR <60 ml/min/1.73m^2 at 2 consecutive visits (15).

How should clinicians manage metabolic complications?

Patients with CKD develop metabolic abnormalities as a result of the kidneys' inability to maintain normal homeostasis as glomerular filtration drops and the kidneys' ability to synthesize hormones declines. The main metabolic complications of concern are hyperphosphatemia and vitamin D deficiency, which lead to secondary hyperparathyroidism, hyperkalemia, and metabolic acidosis.

Vitamin D and phosphorous metabolism

Vitamin D metabolism and phosphate are out of balance in mild CKD, but significant derangements usually occur only after the GFR falls below 30 to 40 mL/min/1.73 m^2 (65–66). Hyperphosphatemia and 1,25-dihydroxyvitamin D deficiency cause hypocalcemia. Hyperphosphatemia, 1,25-dihydroxyvitamin D deficiency, and hypocalcemia induce secondary hyperparathyroidism, which is associated with renal osteodystrophy. Although we lack high-quality studies that show a long-term benefit, guidelines suggest a combination of dietary phosphorous restriction, phosphate binders, and vitamin D supplementation with the goals of maintaining serum calcium and phosphorous within the normal range, treating patients with elevated intact parathyroid hormone levels, and correcting vitamin D [25(OH)D (calcidiol)] deficiency and insufficiency (67–68).

A retrospective nonrandomized cohort study evaluated the effect of calcitriol (a form of vitamin D) in 1418 patients with stage 3 or 4 CKD and hyperparathyroidism (parathyroid hormone level >70 pg/mL). The authors matched calcitriol users to control participants on age, GFR, and time of first indication for calcitriol use. Calcitriol was associated with a decrease in all-cause mortality (hazard ratio, 0.74 [CI, 0.58–0.95]) after adjustment for multiple factors, including age; sex; race; diabetes; coronary heart disease; systolic blood pressure; GFR; and levels of parathyroid hormone, albumin, calcium, and phosphate (69).

Hyperkalemia

Hyperkalemia is a late manifestation of CKD. Mild elevations occur in stage 3, but significant, dangerous elevations usually occur only in stages 4 and 5 (66). Normal levels should be maintained through dietary restriction of potassium. Sodium polystyrene sulfonate resin, which binds potassium in the gut, can be used if necessary. Severe hyperkalemia (typically >6 mEq/L) or hyperkalemic electrocardiographic changes requires urgent action (70). Emergency treatment includes intravenous calcium gluconate initially, intravenous glucose and insulin, intravenous bicarbonate if acidosis is present, and sodium polystyrene sulfonate. If these measure fail, hemodialysis may be needed.

Metabolic acidosis

CKD is associated with metabolic acidosis but, like hyperkalemia, significant acidosis is rare until GFR decreases below 30 mL/min/1.73 m^2 (66). Chronic metabolic acidosis contributes to progression of CKD, insulin resistance, decreased cardiorespiratory fitness, and altered bone metabolism (71). Despite a weak evidence base, guidelines recommend alkali therapy for CKD patients with serum bicarbonate <22 mmol/L to maintain serum bicarbonate levels within the normal range (12).

How should clinicians manage patients with anemia?

Anemia accompanies worsening CKD as kidney production of erythropoietin declines. Anemia is associated with decreased quality of life, left ventricular hypertrophy, and cardiovascular complications in patients with CKD. Although patients with normocytic, normochromic anemia

and a low reticulocyte count are likely to have the anemia of CKD, CKD is not necessarily the sole cause of the anemia. The evaluation of patients with anemia and CKD should include hemoglobin and hematocrit, red blood cell indices, reticulocyte count, serum iron, percentage of transferrin saturation, vitamin B12 and folate levels, and serum ferritin (72). Patients with iron deficiency should be evaluated to identify potential sources of bleeding.

On the basis of studies that show improvement in functional status but not mortality, current guidelines suggest that clinicians consider treating most patients with CKD anemia with erythropoietin when hemoglobin level is between 9 and 10 g/dL. Adequate iron stores are necessary for successful treatment of anemia of CKD because iron is essential for hemoglobin formation and erythropoiesis. Prescribe oral or intravenous iron as needed to maintain adequate iron stores (TSAT >20% and serum ferritin >100 ng/mL). Hemoglobin should not be "normalized," but should be maintained at a level <11.5 g/dL. Targeting higher hemoglobin levels (>13 g/dL) may be associated with increased cardiovascular events (73). Patients with active cancer or a history of stroke should be treated with extra care (72).

In TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy), 4038 patients with diabetes, CKD, and anemia were randomly assigned to darbepoetin-α and a target hemoglobin of 13 g/dL versus placebo with rescue darbepoetin-α when hemoglobin levels dropped below 9 g/dL. There was no difference in the rate of death or cardiovascular events between groups. Although both groups reported improvement in the FACT-Fatigue score from baseline to 25 weeks, the improvement was greater in the darbepoetin-α group. However, when compared with the placebo group, the group that received darbepoetin-α had a hazard ratio for fatal or nonfatal stroke of 1.92 (CI, 1.38–2.68) (74).

How should clinicians treat cardiovascular risk factors?

Physicians must be aware of the elevated cardiovascular risk in patients with CKD and aggressively reduce risk factors for atherosclerosis (3–4). Standard lifestyle recommendations—smoking cessation, 30 minutes of exercise/day most days of the week, alcohol intake limited to 1 drink/day for women and 2 drinks/day for men, and body mass index maintained within the normal range—should be recommended.

In addition to promoting lifestyle measures, cardiovascular risk factors need to be assessed by measuring blood pressure, obtaining a fasting lipid profile, and screening for diabetes. Hypertension and diabetes should be treated. The American College of Cardiology/American Heart Association guidelines for treating high cholesterol should be followed, albeit with a few exceptions: Given the high risk for cardiovascular disease among adults aged 50 years or older with CKD, guidelines recommend treatment with a statin or statin–ezetimibe combination regardless of cholesterol level and do not recommend targeting specific total cholesterol or low-density lipoprotein levels in most patients (75–77).

In the randomized, double-blind SHARP (Study of Heart and Renal Protection) trial, 4650 patients with CKD were assigned to simvastatin 20 mg plus ezetimibe 10 mg daily and 4620 were assigned to placebo. Major atherosclerotic events were reduced by 17% (CI, 6-26) in the simvastatin–ezetimibe group. However, there were no differences noted in rates of nonfatal myocardial infarction or death from coronary heart disease (78).

How should clinicians monitor patients with CKD?

Progression of CKD and its complications (anemia, hyperphosphatemia, secondary hyperparathyroidism, and malnutrition) should be monitored with an an-

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nual assessment of blood pressure; estimation of GFR; and measurement of hemoglobin, serum potassium, calcium, phosphorous, parathyroid hormone, and albumin levels (6, 79–80). More frequent monitoring should be done in patients with moderate to severe CKD (**Figure**); a history of rapid decline in kidney function (>5 mL/min/1.73 m^2 per year); risk factors for faster progression (smoking, poorly controlled hypertension or diabetes, and proteinuria); exposure to a known cause of acute kidney injury, such as radiocontrast dye; or active or changing therapeutic interventions to treat CKD, hypertension, or proteinuria (6, 12).

What are the indications for renal replacement therapy?

Common indications to initiate dialysis are volume overload unresponsive to diuretics, pericarditis, uremic encephalopathy, major bleeding secondary to uremic platelets, and hypertension that does not respond to treatment (30). Hyperkalemia and metabolic acidosis that cannot be managed medically and progressive "uremic" symptoms, such as fatigue, nausea and vomiting, loss of appetite, evidence of malnutrition, and insomnia, are also indications for initiation of renal replacement therapy (30, 81).

When should clinicians consider consulting a nephrologist for treating patients with CKD?

Managing progressive CKD can be an enjoyable challenge for general internists, especially when done in partnership with a nephrologist. Clinicians should consider consulting a nephrologist for managing complications of advanced CKD, such as anemia, bone disease, and hypertension. Clinicians should consult a nephrologist for advanced or complex renal disease for assistance in formulating or implementing a care plan (12). In addition, nephrologists should be involved in therapeutic decision-making about complex acute or chronic glomerular and tubulointerstitial diseases, which often require immunosuppressive therapy.

Clinicians should consult a nephrologist when dialysis is anticipated because a substantial body of observational studies shows a strong association between care by a nephrologist in the months before dialysis and survival on dialysis. As CKD progresses, a nephrologist should be consulted no later than when GFR first declines to <30 mL/min/1.73 m^2 (12). A nephrologist who is well-versed in the technical aspects of renal replacement therapy can discuss treatment methods for ESRD, which may include hemodialysis, peritoneal dialysis, or renal transplantation; provide counseling, psychoeducational interventions, and referral for fistula placement; and initiate dialysis when appropriate (12). With appropriate CKD management and timely referral to a nephrologist, patients with CKD can avoid hospitalizations and either initiate dialysis in the outpatient setting or receive a preemptive kidney transplant.

In a prospective cohort study of 2195 incident dialysis patients, 730 patients were referred to a nephrologist <4 months before initiation of dialysis. This late-referral group had a 44% higher risk for death at 1 year after initiation of dialysis than patients referred earlier than 4 months before starting renal replacement therapy (hazard ratio, 1.44 [CI, 1.15–1.80) (82).

A retrospective analysis of 39 021 Veterans Health Administration clinic users with diabetes and stage 3 or 4 CKD evaluated the association between care by a nephrologist and survival over a median of 19.3 months. Compared with patients who had no nephrology visits, patients with 2, 3, and 5 nephrology visits had adjusted hazard ratios for mortality of 0.80 (CI, 0.67–0.97), 0.68 (CI, 0.55–0.86), and 0.45 (CI, 0.32–0.63), respectively (83).

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Treatment... The main goals in treating CKD are to slow disease progression and prevent cardiovascular complications. To accomplish these goals, blood pressure should be maintained in patients with hypertension and glycemia should be strictly controlled in patients with diabetes. Treating hypertension with ACE inhibitors and ARBs helps preserve renal function. Treating patients with CKD also involves careful management of electrolyte disturbances, secondary hyperparathyroidism, anemia, and malnutrition. As CKD progresses, referral to a nephrologist for assistance in management prepares the patient for renal replacement therapy and may increase survival.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend with regard to prevention, screening, diagnosis and treatment of CKD?

Many of the recommendations included in this review come from the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. All of the KDIGO guidelines are available online at http://kdigo.org/home/guidelines/. Other CKD guidelines are available through the United Kingdom's Renal Associates (www.renal.org), Australia–New Zealand's national kidney guideline group, Caring for Australasians with Renal Impairment (www.cari.org.au), and the Canadian Society of Nephrology (www.csnscn.ca).

What measures do stakeholders use to evaluate the quality of care for patients with CKD?

The National Quality Forum (NQF) has established a number of quality measures (www.qualityforum.org). The following quality measures apply to CKD in adult patients:

1. Percentage of patients younger than 75 years of age with diabetes screened for nephropathy (NQF no. 0062).

2. Percentage of patients with nondiabetic nephropathy treated with ACE inhibitors or ARBs (NQF no. 0621).

3. Percentage of patients with diabetes and hypertension treated with ACE inhibitors or ARBs (NQF no. 0546).

4. Percentage of patients with hypertension with blood pressure controlled to <140/90 mmHg (NQF no. 0018).

5. Percentage of patients with advanced CKD or ESRD receiving erythropoiesis-stimulating agent therapy with a hemoglobin ≤12.0 g/dL (NQF no. 1666).

In the Clinic

Tool Kit

Chronic Kidney Disease

NIH MedLine Plus

www.nlm.nih.gov/medlineplus/ency/article/000471.htm

Information on chronic kidney disease from the NIH.

Guidelines

https://www.kidney.org/professionals/guidelines
https://www.kidney.org/sites/default/files/docs/ckd_evaluation_classification_stratification.pdf
www.nice.org.uk/guidance/cg182/resources/guidance-chronic-kidney-disease-pdf
http://kdigo.org/home/guidelines/ckd-evaluation-management/

Medical guidelines for clinical practice for the diagnosis and treatment of chronic kidney disease.

Patient Resources

http://nkdep.nih.gov/
https://www.kidney.org/kidneydisease/aboutckd
www.mayoclinic.org/diseases-conditions/kidney-disease/basics/definition/con-20026778
http://kdigo.org/home/
www.kidneyfund.org/kidney-disease/chronic-kidney-disease/

National Kidney Disease Education Program with information for patients and caregivers (English).

http://nkdep.nih.gov/inicio.shtml

National Kidney Disease Education Program with information for patients and caregivers (Spanish).

WHAT YOU SHOULD KNOW ABOUT CHRONIC KIDNEY DISEASE

What Is Chronic Kidney Disease?

The kidneys play an important role in keeping the body healthy. They remove waste from the body, balance blood pressure, make important hormones, and help keep bones strong. With chronic kidney disease (CKD), the kidneys gradually stop working. CKD can cause other health problems, like:

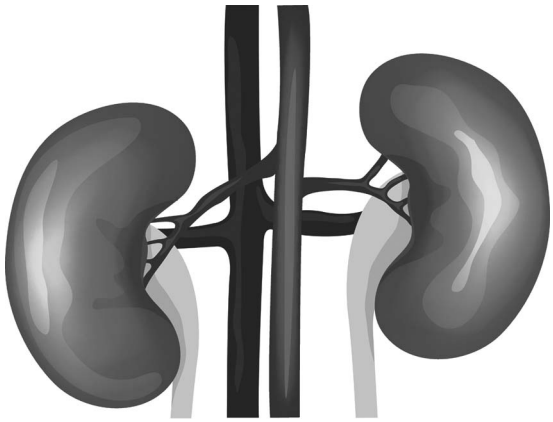
- Heart disease
- Weak bones
- Nerve damage
- Fluid buildup
- Weakened immune system
- Other health problems

CKD is most often caused by diabetes or high blood pressure, but other factors can cause the kidneys to stop working.

What Are the Warning Signs of CKD?

Many people with CKD will not notice symptoms until late in the disease. These symptoms can include:

- Trouble sleeping and tiredness
- Trouble concentrating
- Feeling sick to your stomach or throwing up
- Muscle cramping
- Having no appetite
- Itching
- Swelling in your feet, ankles, or around your eyes



How Is CKD Diagnosed?

Your doctor will ask you about your medical history and any other health problems you have and measure your blood pressure. Your doctor also will check your blood and urine.

How Is CKD Treated?

Treating CKD early can prevent or slow down more damage to the kidneys so that your kidneys keep working. Treatment can include:

- Taking medicine to treat diabetes, high blood pressure, or other health problems that are damaging your kidneys
- Avoiding cigarettes and drugs that may harm your kidneys
- Following a healthy diet and exercising regularly

If your kidneys stop working, dialysis treatment may be needed. Dialysis involves using a tube to connect your body to a dialysis machine for several hours a day on several days each week. The dialysis machine will do some of the work that healthy kidneys do, like removing waste and extra fluids from the body. If your kidneys stop working, kidney transplantation also may be an option.

(*continued on the next page*)

Patient Information

Questions for My Doctor

- How can I stop kidney disease from getting worse?
- What is the best treatment for my chronic kidney disease?
- How does my diabetes or high blood pressure hurt my kidneys?
- Will I ever need dialysis or a kidney transplant?
- Do I need to change my diet or alcohol intake?
- Can I still take the medicines I normally take?
- Are there activities I should avoid?

Bottom Line

- The kidneys are important for keeping the body healthy. With CKD, the kidneys gradually stop working.
- Symptoms of CKD are often not noticed until late in the disease.
- Tests of the blood and urine can help diagnose CKD.
- Treatment includes taking medicine and managing the health problems that damage the kidneys. Dialysis and a kidney transplant are options for people whose kidneys stop working.

For More Information

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National Kidney Foundation
www.kidney.org/kidneydisease/aboutckd
National Kidney Disease Education Program
www.nkdep.nih.gov
American Association of Kidney Patients
www.aakp.org

Patient Information