Diagnosis and Management of Chronic Kidney Disease

JOHN W. GRAVES, MD

On completion of this article you should be able to (1) identify the 3 forms of renal damage that can cause an elevated serum creatinine level, (2) develop a plan for the initial evaluation of the patient with an elevated serum creatinine level, and (3) identify the measures that should be taken to help preserve renal function in patients with an elevated serum creatinine level.

As the US population has continued to age, the number of patients with chronic kidney disease (CKD) has dramatically increased. Faced with this increase, clinicians need a better understanding of what an elevated serum creatinine level represents and a simple codified approach to evaluating renal failure. Creatinine, a muscle waste product, has an imperfect but predictable association with the glomerular filtration rate (GFR). Although other markers of GFR exist, including cystatin C, urea, insulin, and radioisotopic methods, their role in estimating GFR remains a matter for debate, especially that of cystatin C. Diagnosis and management of CKD are challenges for the nonspecialist. We describe a systematic approach that can be used by the nonspecialist to identify most but not all causes of renal insufficiency. Although this approach should allow for earlier recognition of treatable causes of CKD, it does not eliminate the involvement of a nephrologist in the care and management of the conditions causing the renal insufficiency. The nonspecialist should also be able to recognize the 9 therapies that are helpful in preservation of renal function in all patients with CKD.


From the Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.

Individual reprints of this article are not available. Address correspondence to John W. Graves, MD, Division of Nephrology and Hypertension, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (graves.john@mayo.edu).

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Chronic kidney disease (CKD), as defined by a reduction in the estimated glomerular filtration rate (GFR), is increasing in the United States, in part because of the greater prevalence of obesity and hypertension but in greater part because of improved longevity. Because GFR declines 1% per year for every year of life after the third decade, living longer means that it is possible to outlive one’s renal function and to require renal replacement therapy to stay alive. Longevity increases the risk of developing diseases, such as diabetes, hypertension, and atherosclerotic vascular disease, that have direct adverse effects on kidney function. Long life also increases the risk of exposure to nephrotoxic medications for other health conditions, such as arthritis (nonsteroidal anti-inflammatory drugs [NSAIDs]), infections (antibiotics), cancer (chemotherapy), gastroesophageal reflux disease (proton pump inhibitors), and coronary artery disease (radiocontrast agents).

MARKERS OF RENAL FUNCTION

The most commonly used measure of renal function (GFR) in clinical medicine is the serum creatinine level. To use the serum creatinine level as a marker of renal function, creatinine production and protein intake must be assumed to be constant (Figure). Creatinine excretion is due not only to filtration (90%-95%) by the kidney but also to secretion (5%-10%) by the distal tubule. As GFR decreases, the percentage of creatinine excretion due to secretion increases. In this circumstance, substances that block distal tubule secretion of creatinine may cause the serum creatinine level to increase abruptly, when in fact GFR has not changed at all. Because they can confuse the assessment of kidney function, these agents are often avoided in the patient with CKD. Glomerular filtration rate can be estimated by measuring creatinine clearance using serum creatinine levels and a timed urine specimen. However, measuring creatinine clearance is time-consuming and fraught with errors of timing and collection, so other methods of estimating GFR, both those that rely on determining serum creatinine levels and those that do not, have been sought to replace the measured creatinine clearance.

Multiple formulas exist to estimate renal function accurately by correcting for such factors as differences in muscle mass in men vs women or in African American vs white people and changes in muscle mass due to aging. The most commonly used are the Cockcroft-Gault equation and the 4-variable and 6-variable Modification of Diet in Renal Disease (MDRD) equations. Rule et al have argued that, because these formulas are derived from patients with renal disease, they may not predict renal function as well in patients without renal disease. Most clinicians use the MDRD equation because of its availability on the Internet, where one can simply plug in values for age, weight, race, and sex to receive an estimated GFR. It should be recognized that all these formulas have wide confidence intervals such that small changes in true GFR are hard to detect by this method.
An alternative serum marker, cystatin C, has been proposed as a marker of GFR. Cystatin C, an endogenous cysteine protease inhibitor, is freely filtered by the kidney and unaffected by renal tubules. However, serum levels are more variable than for creatinine, and the fact that serum levels can be affected by acute disease (malignancy, infection with human immunodeficiency virus) has left cystatin C without a defined role in clinical medicine. Estimates of GFR can be obtained from radioisotope and short clearance studies using infused substances, such as inulin or iothalamate. These tests, which are too complex for regular clinical use, are not required because the estimated GFR serves the clinician well in most circumstances. Their primary clinical function is to help define whether a patient is at end-stage renal disease. All these estimates of renal function are harder to interpret during acute renal failure, which is characterized by an unstable association between creatinine production and renal excretion (changing renal function).

Where does the primary care physician find the previous measurements of serum creatinine levels that are needed to interpret the current value correctly? Sources of baseline serum creatinine values include laboratory work performed during previous physician visits, minor surgeries (appendix, tonsillectomy), physical examinations at the workplace or for purposes of insurance, and school or sports physical examinations, during which routine urinalysis is often performed to help ascertain the onset of kidney disease (proteinuria or microhematuria). Once it has been determined that the elevated serum creatinine level represents CKD, an effective approach is needed for identifying why such an increase occurred.

**TYPES OF RENAL FAILURE**

The first task in evaluating the patient with an elevated creatinine level is to categorize the patient’s clinical presentation as 1 of 3 possible types of renal failure: postrenal failure, prerenal azotemia, or intrinsic renal failure.

**POSTRENNAL FAILURE**

The astute clinician will always start with this mechanism of renal failure because it may be the most reversible form of renal failure and should never go undiagnosed. The first and most common type of postrenal failure is obstructive uropathy. Obstructive uropathy can be caused by intrinsic obstruction of urinary flow (eg, stone, tumor, blood clot, or papillary necrosis) or by extrinsic obstruction (eg, postoperative, prostatic hypertrophy, retroperitoneal fibrosis, retroperitoneal tumor [lymphoma or metastatic disease]). The second and much less common form of postrenal failure is renal vein thrombosis. Renal vein thrombosis can present as acute kidney failure with flank pain and gross hematuria. Renal vein thrombosis may also present as a chronic condition without the dramatic acute symptoms, often in the setting of glomerulonephritis. In adults, it usually occurs in association with a coagulopathy from an acute illness, such as metastatic malignancy or acute glomerulonephritis. Renal vein thrombosis is more common in children than adults and is associated with diseases that cause volume contraction.

**PRERENAL AZOTEMIA**

Prerenal azotemia, another of the reversible forms of CKD, results from a reduction in perfusion to the kidney that leads to renal dysfunction and an elevated serum creatinine level. It can be characterized by events such as acute renal artery embolism, dissection, and thrombosis; however, it is more commonly associated with other causes of decreases in effective circulating volume (Table 1). In many patients with CKD, a prerenal component presents as a further

![Diagram showing the balance between muscle production and renal excretion of serum creatinine. As the glomerular filtration rate decreases, the percentage of creatinine excreted via secretion increases.](image-url)

**TABLE 1. Causes of Prerenal Azotemia**

<table>
<thead>
<tr>
<th>Cause</th>
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<tbody>
<tr>
<td>Low cardiac output</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td>Chronic heart failure</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Decreased plasma volume</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Sweating</td>
</tr>
<tr>
<td>Nasogastric suction</td>
</tr>
<tr>
<td>Burns</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Decreased hemoglobin levels</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Endocrine dysfunction</td>
</tr>
<tr>
<td>Uncontrolled diabetes mellitus (polyuria)</td>
</tr>
<tr>
<td>Diabetes insipidus</td>
</tr>
<tr>
<td>Addison disease</td>
</tr>
<tr>
<td>Renal dysfunction</td>
</tr>
<tr>
<td>Salt-wasting nephropathy</td>
</tr>
<tr>
<td>Vasodilatation</td>
</tr>
<tr>
<td>Sepsis syndrome</td>
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<tr>
<td>Endotoxemia</td>
</tr>
</tbody>
</table>

FIGURE. Balance between muscle production and renal excretion of serum creatinine. As the glomerular filtration rate decreases, the percentage of creatinine excreted via secretion increases.
increase in serum creatinine levels from previous baseline values. History and physical examination are critical for identifying prerenal azotemia. The clinician should seek evidence in the patient’s history of nausea, vomiting, diarrhea, new use or increased dose of diuretics, unexpected resolution of long-standing edema, weight loss, or orthostatic symptoms. During the examination, lying and standing blood pressure and pulse are the most important tools to evaluate for extracellular volume depletion. Chronic heart failure, liver disease, and the nephrotic syndrome have the appearance of volume overload (eg, edema, rales, abdominal fluid wave), yet the kidney behaves as if there were volume depletion, potentially resulting in an elevated serum creatinine level.

A number of urinary markers, among which fractional excretion of sodium (FENa) is the most prominent, have been proposed for identifying the patient with oliguric prerenal azotemia. However, in some circumstances, FENa may be falsely low, suggesting prerenal azotemia, when it is not the cause of the elevated serum creatinine level. When is the case among patients with glomerulonephritis, myoglobinuric renal failure, contrast-induced nephropathy, renal allograft rejection, acute interstitial nephritis, or urinary tract obstructions and among patients who have been prescribed diuretics to augment urine output. Because FENa may be falsely low in some patients and because many hours may be required to obtain the data needed for its calculation, a thorough history and examination are favored for detecting volume contraction over the FENa. Other laboratory findings that may aid in the diagnosis of prerenal azotemia include elevated levels of serum uric acid and serum calcium and an increase in the ratio of blood urea nitrogen to serum creatinine to more than 20.

**Intrinsic Renal Failure**

The third and final cause of an elevated serum creatinine level involves disease of the renal tissue itself. There are 3 types of tissue in the kidney: glomerular tissue (primary glomerular disease; secondary glomerular diseases due to other conditions [eg, systemic vasculitis, diabetes, hypertension, amyloidosis]); vascular tissue, which may be affected by systemic vasculitides, atheroemboli, and thromboemboli; and interstitial tissues, which can be damaged by sickle cell anemia, chronic analgesic use, and certain medications (eg, antibiotics, proton pump inhibitors, NSAIDs).

As Table 2 shows, one can begin to identify which type of renal parenchymal problem is present with 4 pieces of simple information: findings on urine microscopy, results of a 24-hour protein excretion test, presence of hypertension, and time course of the elevated serum creatinine level.

<table>
<thead>
<tr>
<th>Urinalysis</th>
<th>Glomerular</th>
<th>Vascular</th>
<th>Interstitial</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC cast, OFB, fatty cast</td>
<td>RBC cast</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>24-h protein excretion (g/d/1.73 m²)</td>
<td>&gt;3.5</td>
<td>1-5</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>50%</td>
<td>75%</td>
<td>Rare</td>
</tr>
<tr>
<td>Rate of increase in serum creatinine level</td>
<td>&lt;1 y</td>
<td>&gt;15-20 y</td>
<td></td>
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</table>

Urine Microscopy. Urine microscopy, the “poor man’s renal biopsy,” provides valuable information only if the urine specimen is fresh (<20 minutes from voiding) and is analyzed by a physician (ie, a nephrologist) who is able to recognize red blood cell (RBC) casts. At any clinical laboratory, urine samples are analyzed in batch form; by the time a technician looks at the specimen, the cast will have degraded and be undetectable. The presence of more than 25 dysmorphic RBCs is a common surrogate for RBC casts. Red blood cells that have traversed the glomerular basement membrane to reach the urinary space (glomerulonephritis) will have a distorted appearance because of that transit. In contrast, RBCs entering the urine from other parts of the urinary tract will not be distorted and so will be unimorphsic. Although the use of this surrogate is accepted practice, careful evaluation shows that dysmorphic RBCs are no more suggestive of glomerulonephritis than is plain hematuria in the presence of substantial proteinuria.

This point is critical because urinary microscopy aids identification of the type of renal disease only by showing whether RBC casts (nephritis) or oval fat bodies, fatty casts, and free fat (nephrosis) are present. As shown in Table 2, RBC casts are seen in glomerular disease and vasculitis of the kidney but not in interstitial disease. All other findings of urine microscopy—eg, ropey casts, hyaline casts, waxy casts, renal tubular epithelial cells—are nonspecific reflectors of renal disease and are of no help to the clinician in determining the specific cause of CKD.

**24-Hour Urinary Protein Excretion Test.** By definition, 24-hour urinary protein excretion in patients with glomerular disease (eg, nephrotic syndrome) is at least 3.5 g/d per 1.73 m² but can be much higher. Although substantial proteinuria (1-5 g/d per 1.73 m²) is often associated with vasculitis, proteinuria is more pronounced in primarily glomerular forms of renal disease. Interstitial renal disease usually presents with little or no proteinuria; however, up to 2 g of urinary protein, primarily tubular or Tamm-Horsfall protein, may be excreted daily.

Hypertension. Hypertension, especially when it occurs early in the course of renal failure, can be useful in evaluating intrinsic forms of kidney disease. Most patients with...
vasculitis of the kidney will have hypertension, often severe. Early in the disease process, patients with glomerulonephritis are slightly less likely to be hypertensive than those with vasculitis. Patients with interstitial forms of renal disease develop hypertension only as they near end-stage renal disease.

**Time Course of Increase in Serum Creatinine Level.**
When available, the time course of the increase in the serum creatinine level is very helpful in identifying the type of renal disease causing its elevation. When left untreated, vasculitis of the kidney and diseases such as Goodpasture syndrome, Wegener granulomatosis, and lupus vasculitis rapidly progress to renal failure, reaching end stage or requiring dialytic support within weeks or months of the beginning of the disease. Although untreated glomerulonephritis may have a rapid course, renal failure usually develops more slowly, with low levels of GFR reached in a period of 2 to 10 years. Interstitial renal disease has a more indolent course, reaching low levels of GFR only after 10 to 20 years. However, a rapidly increasing serum creatinine level is possible with allergic interstitial nephritis and acute tubular necrosis.

**EVALUATION OF THE PATIENT**

**History**
In taking the history of a patient with CKD, the clinician should attempt to determine when the onset of proteinuria and hypertension occurred and whether previous serum creatinine tests have been performed. Patients should also be questioned regarding voiding symptoms, such as hesitancy, decreased stream strength, or intermittent large and small voiding amounts, because these symptoms suggest obstructive uropathy. Every patient with an elevated serum creatinine level should be asked if they have a history of diabetes, arthritis, or medication exposure. Almost all NSAIDs, including over-the-counter forms and almost all antibiotics, have been reported to cause renal failure in at least 1 case report. In fact, no NSAID can be declared “safe” with regard to renal failure. Previous use of chemotherapeutic agents, such as gemcitabine and cisplatin, or history of gastroesophageal reflux disease and proton pump inhibitor use should be identified. Recent radiographic studies using radiopaque agents should also be considered when attempting to identify possible causes of an elevated serum creatinine level.

**Diagnostic Examination**
The diagnostic examination for the patient with renal failure includes a few unique items. First, to test for prerenal azotemia, lying and standing blood pressure and pulse should be recorded. Funduscopic examination for findings of hypertension (Keith-Wagener-Barker) and diabetic changes should be performed. The ability to view the nondilated fundus is greatly enhanced with the use of a specially designed ophthalmoscope (PanOptic; Welch Allyn, Skaneateles Falls, NY). During an examination specific to a diagnosis of increasing serum creatinine levels, the clinician should also check for evidence of volume overload (rales, third heart sound, lower-extremity edema), joint effusions or erythema, and splinter hemorrhages, as well as palpate for distended bladder above the symphysis pubis.

**Laboratory Testing**
**Standard.** Consider testing for creatinine phosphokinase and aldolase levels to determine that the elevated serum creatinine level retains its validity as a marker of renal function and does not reflect increased creatinine production (eg, rhabdomyolysis).

The standard work-up also includes a physician-performed urinalysis; measurement of levels of serum creatinine (usually with a full electrolyte panel), creatinine, and serum cholesterol (nephrotic syndrome); and a 24-hour urinary protein excretion test.

**Subspecialty Evaluation.** To determine whether systemic illness is the cause of renal disease, an antineutrophil cytoplasmic antibody panel, serum and urine protein electrophoresis, and fat aspiration for amyloidosis may be performed, as should serologic tests to determine C3 and C4 complement levels and to check for the presence of anti-nuclear antibody, rheumatoid factor, antilgmolomlar basement membrane antibody, and cryoglobulins. Although commonly performed, these tests only rarely reveal a systemic disease thought to be present without the serologic evidence, and even positive serologic findings do not obviate the need for renal biopsy. However, positive serologic findings may make physicians more comfortable in recommending a renal biopsy. Although most renal biopsies are without incident, 50% of the patient’s GFR could be lost if refractory bleeding requires nephrectomy.

**Radiography**
Renal ultrasonography with arterial Doppler studies is the single most important test for evaluating all patients with an elevated creatinine level. First and most importantly, it is the least invasive method for identifying obstructive uropathy, the most reversible form of renal failure. Second, it provides information on renal size. If the kidneys are smaller than 7 to 8 cm, then the likelihood of a reversible form of renal failure is extremely low. Large kidneys (>12-13 cm) have a specific differential diagnosis, including reversible conditions such as acute glomerulonephritis, infiltrative diseases of the kidney (leukemia, lymphoma, Hodgkin disease, multiple myeloma, and amyloidosis), and
conditions without reversibility such as diabetic nephropathy, polycystic kidney disease, and obstruction. The Doppler component helps identify patients with bilateral renal artery stenosis, whose renal function would benefit from successful angioplasty.

**PRESERVING RENAL FUNCTION IN CKD**

Regardless of the renal process, patients with renal failure can and should be managed aggressively with a 9-pronged approach (Table 3). If primary care physicians actively pursue this approach, they can substantially reduce the rate of GFR decline and delay the need for dialysis or renal transplant. Aggressive blood pressure reduction has always been shown to protect the kidney from further damage. The use of antihypertensive agents with antiproteinuric properties is also important but does not supersede the need to reach goal blood pressure. When blood pressure is well controlled, additional therapy (adding an angiotensin receptor blocker to an angiotensin-converting enzyme inhibitor or increasing doses of either) with resultant reduction in quantitative proteinuria has also been shown to benefit patients with CKD and proteinuric renal disease.23 Good diabetes control can slow the rate of progression of diabetic nephropathy. Reduction in low-density lipoprotein cholesterol to less than 100 mg/dL (to convert to mmol/L, multiply by 0.0259) not only reduces the risk of vascular disease, which is very high in these patients, but also provides some degree of renal protection.24 Although the low-protein diet has never been shown to be beneficial in reducing the rate of GFR decline in humans,25 it is often still recommended. The low-protein diet is counterintuitive as a means of slowing the rate of GFR decline: if patients reduce their protein intake, they replace that caloric intake with fat and glucose that accelerate their vascular disease development.26 Unless they refuse dialysis or transplant, patients do not die of renal failure; however, they do die of acute myocardial infarction or stroke, often before reaching end-stage renal disease,4 and thus the American Heart Association diet, which is low in fat and salt (for blood pressure control), is preferred. Patients with renal disease may be overwhelmed with the many major modifications in lifestyle that they are asked to make. By focusing their attention on the most important modifications, such as smoking cessation, and deemphasizing low-priority modifications, such as the low-protein diet, better results may be obtained.27

**CONCLUSION**

Identifying the cause of an elevated serum creatinine level can be challenging. The systematic approach should greatly assist clinicians in identifying those causes. Although referral to a nephrologist will sometimes still be necessary, this approach should make the patient and primary care physician better able to understand what issues the nephrologist may need to address to evaluate the elevated serum creatinine level. If the renal failure becomes chronic, the primary care physician can help the patient maintain long-term renal function by encouraging adherence to the 9-pronged treatment approach.

### REFERENCES

CME Questions About Chronic Kidney Disease

1. Which one of the following is the most important test for prerenal azotemia?
   a. Fractional excretion of sodium (FENa)
   b. 24-hour urinary protein excretion
   c. Lying and standing blood pressures
d. Elevated blood urea nitrogen to creatinine ratio
e. Elevated uric acid level

2. Which one of the following is not used to decide which renal tissue is involved in a patient with intrinsic renal failure?
   a. Presence of hypertension
   b. Findings on urine microscopy
   c. Results of 24-hour urinary protein excretion test
d. Results of 24-hour urinary creatinine excretion test
e. Duration of elevated serum creatinine level

3. Which one of the following capabilities of renal ultrasonography is not helpful in evaluating the patient with an elevated creatinine level?
   a. Diagnosing obstructive uropathy
   b. Identifying patients with cysts in the kidney
c. Providing size of the kidneys
d. Detecting renal artery stenosis by Doppler
e. Providing evidence of infiltrative disease

4. A 45-year-old man presents with a history of headaches and recent development of fatigue and hypertension. Previous medical records show that his past serum creatinine values were 1.0 mg/dL in 1976, 1.3 mg/dL in 1979, and 2.3 mg/dL in 1984. At presentation, his serum creatinine value is 6.1 mg/dL. On examination, he is found to have hypertension (blood pressure, 170/100 mm Hg) and grade 1 Keith-Wagener-Barker hypertensive funduscopic changes; findings on the rest of the examination are normal. The patient’s total cholesterol is minimally elevated at 220 mg/dL (to convert to mmol/L, multiply by 0.0259), and urinary protein excretion rate is 210 mg/d per 1.73 m². Urine microscopy reveals rare red blood cells (RBCs), white blood cells, and no casts or dysmorphic RBCs. Ultrasonography shows 7-cm kidneys. The patient is taking 25 mg of hydrochlorothiazide orally once daily, 250 mg of α-methyldopa twice daily, and fiorinal as needed for headaches. Which one of the following is the most likely diagnosis for this patient?
   a. Prerenal azotemia
   b. Postrenal failure
c. Chronic interstitial nephritis (from analgesic use)
d. Wegener granulomatosis
e. Goodpasture syndrome

5. Which one of the following is not a prerequisite for using serum creatinine levels as a marker of glomerular filtration rate (GFR)?
   a. Stable creatinine production
   b. Stable dietary protein intake
c. 5% of creatinine excretion due to tubular secretion
d. Patient not in acute renal failure
e. Age older than 10 years