



EDUCATIONAL OBJECTIVE: Readers will interpret the glomerular filtration rate appropriately

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Interpreting the estimated glomerular filtration rate in primary care: Benefits and pitfalls

ABSTRACT

As several equations have been developed for estimating the glomerular filtration rate (GFR), many laboratories are now reporting the GFR automatically, and primary care providers are left trying to interpret the results and put them into the context of patient care. Therefore, it is important that health care professionals understand how to interpret the estimated GFR value and how to recognize when the estimate may not be accurate.

KEY POINTS

Chronic kidney disease must be detected in its early stages so that measures can be taken to detect its complications and to delay its progression to kidney failure.

The creatinine concentration is an imperfect marker of renal function and should not be used by itself in assessing renal function.

Formulas for estimating the GFR from the serum creatinine level along with other easily obtained variables continue to be refined.

Primary care physicians and nephrologists need to collaborate to provide the optimal care for patients with chronic kidney disease.

CHRONIC KIDNEY DISEASE is most often discovered and diagnosed by primary care providers. The equations for estimating the glomerular filtration rate (GFR) facilitate earlier detection of this disease. However, the estimated GFR must be interpreted in the context of the individual patient. The diagnostic criteria and staging of chronic kidney disease must be understood so that it can be recognized and managed at the earliest possible stage. In this way, primary care physicians and nephrologists can better coordinate the care of these patients.

THE STAGES OF RENAL DISEASE AND THE GFR

Before 2002, an organized approach to the clinical management of patients with renal dysfunction was hampered by a lack of a standardized way to define this condition. This changed when the National Kidney Foundation, through the Kidney Disease Outcomes Quality Initiative (K/DOQI),¹ defined the stages of chronic kidney disease based on the GFR as estimated by the Modification of Diet in Renal Disease (MDRD) equation.^{2,3}

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This system has increased the recognition of chronic kidney disease by the health care community and the general public. But the entire system hinges on the utility, accuracy, and reliability of the equations used to estimate the GFR.

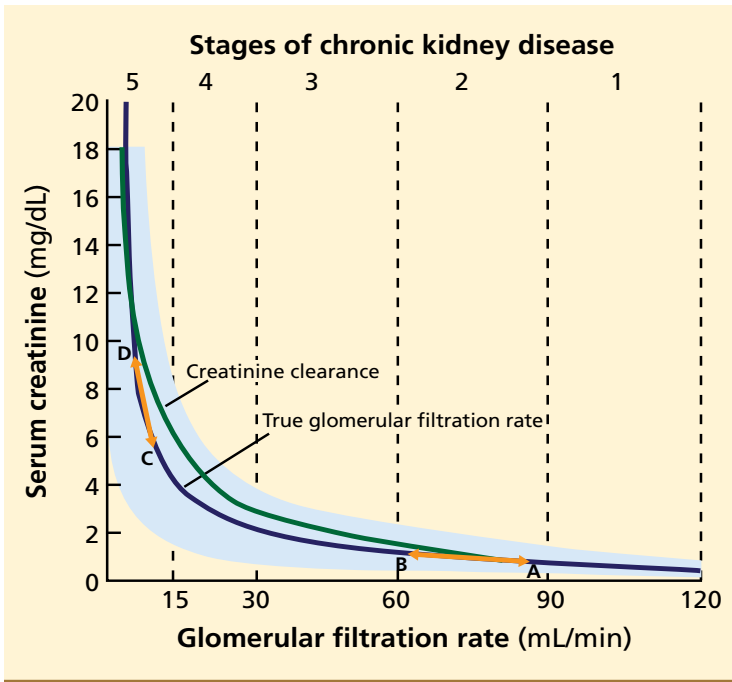


FIGURE 1. The relationship between serum creatinine concentration, creatinine clearance, and glomerular filtration rate (GFR), shown with a 95% confidence interval (blue band). Points A and B illustrate the large change in GFR that results from a small change in serum creatinine at higher levels of kidney function. Points C and D illustrate the small change in GFR that results from a large change in serum creatinine at lower levels of kidney function. Creatinine clearance tends to overestimate the GFR.

BASED ON 823 PATIENTS SEEN AT CLEVELAND CLINIC; DATA PRESENTED IN ROLIN HA III, HALL PM. EVALUATION OF GLOMERULAR FILTRATION RATE AND RENAL PLASMA FLOW. IN: JACOBSON HR, STRIKER GE, KLAHR S, EDITORS. THE PRINCIPLES AND PRACTICE OF NEPHROLOGY, 2ND ED. ST. LOUIS: MOSBY-YEAR BOOK, INC., 1995: 8-13.

In this article, we review the concepts of renal clearance and how to interpret the GFR in healthy patients and in those with chronic kidney disease. The following cases illustrate the interpretation of GFR in the context of patient care.

■ CASE 1: A 60-YEAR-OLD WOMAN WITH A 'NORMAL' CREATININE LEVEL

A 60-year-old white woman with no significant medical history has routine laboratory tests done as part of her annual physical examination. She weighs 135 pounds (61.2 kg) and is 64 inches (163 cm) tall. Her serum creatinine level is 1.1 mg/dL; her estimated GFR is 53 mL/min/1.73 m². A urine dipstick test for protein and blood is normal.

■ CASE 2: PROTEINURIA WITH A PRESERVED GFR

A 20-year-old African American man with no medical history is undergoing routine blood testing. His serum creatinine level is 1.1 mg/dL; his estimated GFR is reported as “> 60 mL/min/1.73 m²” (calculated at 109 mL/min/1.73 m²). He is 72 inches (183 cm) tall and weighs 180 pounds (83.0 kg); he lifts weights four times a week. Urine dipstick testing reveals 3+ proteinuria.

■ SERUM CREATININE: AN IMPERFECT MARKER OF KIDNEY FUNCTION

Of the various functions of the kidney, the ability of the glomeruli to filter the blood, as assessed by the GFR, is considered the best index of overall kidney function.^{4,5} The GFR can be thought of as the clearance of a substance from the plasma by the kidney in a period of time. This is useful because no method is available to routinely and directly measure filtration across the glomerular basement membrane.

Substances that are cleared by the kidney are used to estimate the GFR. The ideal substance for this estimate is one that is cleared only by filtration and not through metabolism or excretion by other means.

The urinary clearance of the exogenous substance inulin is considered the gold standard method, but radioisotopes such as iothalamate and other markers have replaced inulin in clinical laboratories. Because these methods are expensive, time-consuming, and not widely available, alternative methods that use endogenous markers such as creatinine have been developed for clinical practice.

The serum creatinine concentration possesses many of the qualities of an ideal marker for estimating kidney function. Creatinine is produced by the body at a relatively constant rate under normal conditions and is easy and inexpensive to measure. However, it has several limitations:

- Its clearance does not solely reflect glomerular filtration because the renal tubules also excrete it into the urine.⁶ As a result, creatinine clearance (see below) will tend to overestimate the GFR (FIGURE 1).

TABLE 1

Factors that can alter the serum creatinine level without changing the glomerular filtration rate

FACTOR	MECHANISM	RECOMMENDATION
Muscle mass	High muscle mass increases creatinine; muscle wasting decreases it	
Dietary protein intake	Diets heavy in meat or protein supplements can increase the creatinine level; vegetarian diets may decrease it	Stop protein supplements before laboratory samples are drawn
Exercise	Strenuous exercise (eg, weight-lifting) can cause muscle breakdown and creatinine release, elevating serum creatinine	Avoid strenuous exercise before laboratory samples are drawn
Cimetidine, trimethoprim	Block tubular secretion of creatinine, raising serum creatinine levels	
Fibrates	Unclear; possibly increase creatinine production by muscles	Hold medication until laboratory samples are drawn
Flucytosine, praline, hemoglobin	Falsely increase the creatinine value by interfering with enzymatic assays for it	
Metamizol, methyldopa, ethamsylate	Falsely decrease the creatinine value by interfering with enzymatic assays for it	

- The serum creatinine concentration is directly dependent on muscle mass, which varies with sex (women tend to have less muscle mass as a percent of body weight than men), age (muscle mass decreases with age), and race (African Americans have a higher serum creatinine level for the same GFR than other Americans).⁶ Thus, there is no “normal” value for serum creatinine that applies to all patients.
- Other factors can alter the creatinine level without changing the GFR, such as changes in dietary protein intake, exercise, and drugs such as cimetidine⁷ and fibrates⁸ (TABLE 1).

Another important point is that the relationship between the serum creatinine concentration and the GFR is parabolic.⁹ At high kidney function, large changes in the GFR are reflected by very small changes in serum creatinine—the GFR must fall quite a bit before the serum creatinine level rises very much (points A to B in FIGURE 1). At lower kidney function, small changes in GFR are reflected by large changes in serum creatinine (points C to D in FIGURE 1). This phenomenon can cause physicians to view small changes in creatinine as unimportant in patients with cre-

atinine levels in the normal or near-normal range. Conversely, small changes may be due to random error inherent in the methods of measuring creatinine rather than to changes in kidney function.

Because the serum creatinine concentration by itself may be misleading when estimating GFR, the National Kidney Foundation and the National Kidney Disease Education Program recommend that it not be used on its own to estimate kidney function.

■ ESTIMATING THE GFR

Measuring 24-hour creatinine clearance

Measuring 24-hour creatinine clearance involves measuring the concentrations of creatinine in the serum and the urine and the volume of urine excreted in 24 hours.

The 24-hour creatinine clearance was long considered the best alternative to the serum creatinine concentration for assessing kidney function, as it adjusts for changes in the creatinine concentration by taking into account creatinine’s excretion in the urine. However, 24-hour urine collection is burdensome for the patient, and the results are not always reliable

TABLE 2

Risk factors for chronic kidney disease

Age > 60 years
 Cardiovascular disease
 Diabetes mellitus
 Exposure to nephrotoxic drugs
 Family history of chronic kidney disease
 Hepatitis C infection
 Hyperlipidemia
 Hypertension
 Male sex
 Obesity
 Malignancy
 Metabolic syndrome
 Tobacco use
 US minority status

BASED ON INFORMATION IN GO AS, CHERTOW GM, FAN D, MCCULLOCH CE, HSU CY. CHRONIC KIDNEY DISEASE AND THE RISKS OF DEATH, CARDIOVASCULAR EVENTS, AND HOSPITALIZATION. N ENGL J MED 2004; 351:1296–1305.

People with greater muscle mass produce more creatinine

because of variations in collection technique. Also, using the creatinine clearance does not resolve problems with using the serum creatinine concentration, such as tubular secretion and overestimation of GFR.

In an effort to more easily estimate GFR from blood tests alone, efforts to develop mathematical equations that more closely estimate GFR began over 40 years ago. These equations take into account factors such as age, sex, and ethnicity. The best known of these are the Cockcroft and Gault¹⁰ and the MDRD equations.⁵

The Cockcroft-Gault equation

The Cockcroft-Gault equation is fairly simple, using serum creatinine, ideal body weight, and an adjustment factor for sex. Its main drawbacks are that it was developed to model creatinine clearance, itself an imperfect estimation of GFR, and it depends heavily on the accuracy of the value for “lean” body weight used in the equation.

The MDRD equation

The MDRD equation has now largely re-

placed the Cockcroft-Gault equation. Developed using iothalamate GFR measurements, it therefore estimates GFR rather than the less-accurate creatinine clearance. Also, it is normalized to a standard body surface area (1.73 m²), obviating the need to determine ideal body weight.

Since the estimated GFR can often be calculated using data available in most electronic medical record systems, it can be reported directly with any laboratory report that includes a serum creatinine value.

The main drawback of the MDRD equation is that it tends to underestimate GFR at higher ranges of kidney function, ie, higher than 60 mL/min/1.73 m².^{3,11}

The CKD-EPI equation

The Chronic Kidney Disease Epidemiology Collaboration study (CKD-EPI) equation,¹² published in 2009, is expected to eventually replace the currently used MDRD equation, as it performs better at higher ranges of GFR.

Although the CKD-EPI equation still lacks precision and accuracy, it underestimates GFR to a lesser degree than the MDRD equation in patients with preserved renal function. Also, it was developed with the objective of reporting a specific value even when the estimated GFR is greater than 60 mL/min/1.73 m². (In contrast, when laboratories use the MDRD equation, the recommendation is to report any value above this level as “greater than 60 mL/min/1.73 m²”).

A limitation of all equations that use the serum creatinine concentration to assess kidney function is the assumption that creatinine production is both stable over time and similar among patients. As a result, these equations should not be used in situations in which renal function is changing rapidly, such as in acute kidney injury. Also, they should be used with caution in patients at the extremes of body mass, since they underestimate GFR in very muscular patients (eg, as in case 2) and overestimate GFR in very small patients (eg, as in case 1).

Calculators for estimating the GFR using these equations are available on many Web sites (see www.kidney.org/professionals/kdoqi/gfr_calculator.cfm).

■ SCREEN EVERYONE AT RISK

As most patients with established medical problems have blood drawn periodically for routine chemistry panels, the diagnosis of chronic kidney disease often occurs through routine testing. For patients who do not yet carry this diagnosis, it is important to recognize the risk factors for chronic kidney disease (TABLE 2) and to determine who should be screened.

In general, anyone at higher risk of chronic kidney disease should be screened for it. This group includes US minorities and patients with hypertension, cardiovascular disease, and diabetes mellitus, among others.¹³ Screening includes an assessment of estimated GFR and urinalysis for proteinuria or hematuria.

■ CHRONIC KIDNEY DISEASE DEFINED: DAMAGE AND DURATION

The definition of chronic kidney disease contains two components—kidney damage and duration (TABLE 3).¹

The kidney damage can be either parenchymal renal damage independent of GFR (for example, cystic disease, glomerular hematuria, or proteinuria) or depressed GFR independent of evidence of parenchymal renal disease (an estimated GFR of less than 60 mL/min/1.73 m²).

The duration component requires that the abnormality be present for at least 3 months (ie, chronic).

Concerns about the definition

This definition has not been without controversy.

An unintended consequence of not reporting estimated GFR values above 60 mL/min/1.73 m² in absolute numbers is that providers may ignore changes in serum creatinine at estimated GFRs in this range, as they assume that the kidney function is “normal.” This may change in the future if the CKD-EPI equation is used, which produces less bias at slightly higher GFRs.

Providers may also tend to focus solely on the estimated GFR criterion and ignore other evidence of chronic kidney disease, such as abnormalities in urinalysis or imaging studies. For example, proteinuria has been shown to

TABLE 3

Definition, stages of chronic kidney disease

Definition of chronic kidney disease

Either

Kidney damage lasting at least 3 months regardless of glomerular filtration rate (GFR), on the basis of biopsy or abnormal blood, urine, or radiographic tests

or

GFR < 60 mL/min/1.73 m² for 3 or more months regardless of evidence of kidney damage

Stages of chronic kidney disease

1	Kidney damage	and	GFR ≥ 90 mL/min
2	Kidney damage	and	GFR 60–89 mL/min
3	Moderate		GFR 30–59 mL/min
4	Severe		GFR 15–29 mL/min
5	Kidney failure, end-stage renal disease		GFR < 15 mL/min

ADAPTED 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):S1–S266, WITH PERMISSION FROM ELSEVIER, [HTTP://WWW.SCIENCEDIRECT.COM/SCIENCE/JOURNAL/ 02726386](http://www.sciencedirect.com/science/journal/02726386).

be more important than absolute GFR values in predicting progression of renal dysfunction and cardiovascular risk.¹⁴ Proteinuria, especially in the setting of an estimated GFR above 60 mL/min/1.73 m², can be missed if not screened for and underappreciated once found.

Moreover, in elderly patients, the current GFR equations underperform at borderline GFR values and can yield depressed values even at impressively “normal” serum creatinine levels. As a result, there is concern that chronic kidney disease is being overdiagnosed under the current system. This is especially worrisome in elderly white women without risk factors for chronic kidney disease (eg, as in case 1).

In addition, the question arises whether the arbitrary cutoff for chronic kidney disease—60 mL/min/1.73 m²—applies to all populations.^{15,16} The utility of classifying someone as having chronic kidney disease who has an estimated GFR of 55 mL/min/1.73 m² and no risk factors for chronic kidney disease (TABLE 2)

should be questioned if the risk of progressing to end-stage renal disease or suffering a cardiovascular event is only minimally higher than in patients with a higher estimated GFR.^{6,17} If the true purpose of developing the chronic kidney disease classification system is to improve patient care and outcomes, then it is of no benefit to overclassify such patients. Indeed, the stress induced by the diagnosis and the negative implications on insurance coverage and health care costs may outweigh any benefits.¹⁸

Nevertheless, these concerns do not invalidate the entire chronic kidney disease definition system, but have stimulated current efforts to improve it based on outcomes research.¹⁹

■ CASES REVISITED

Case 1: Problems with estimating GFR in a small woman

Case 1 has several points to note.

The patient's small body size reflects low-level creatinine production. It is not atypical to find serum creatinine levels of 0.5 mg/dL in such patients. Thus, her serum creatinine level of 1.1 mg/dL may be abnormal. The fact that the MDRD equation "normalizes" the result to 1.73 m² of body surface area in patients with very low muscle mass will lead to an overestimation of GFR. However, she has no risk factors for chronic kidney disease.

Additionally, in up to two-thirds of patients kidney function declines with age.²⁰ Whether or not this is "normal aging" of the kidney, it is not clear that this decline in GFR reflects an underlying pathologic process.

Finally, since the patient is an older white woman, the estimated GFR tends to underestimate the true GFR. So while her body size may predispose to an overestimation of GFR, her age, race, and sex predispose to an under-

estimation of GFR. Many nephrologists would simply order urinalysis and ultrasonography to rule out other evidence of renal dysfunction, then recommend routine monitoring of kidney function in this case.

Case 2: Proteinuria is not normal

In case 2, because the patient is African American, young, and male, his creatinine level yields a higher estimated GFR than in case 1, despite having the same value. However, his estimated GFR still underestimates his true GFR because of his greater creatinine production due to his muscular physique.

This patient subsequently underwent iothalamate GFR testing, which yielded a GFR of 115 mL/min/1.73 m². However, he has dipstick-positive proteinuria, which, if confirmed on further testing, would meet the criteria for chronic kidney disease and put him at a higher risk of cardiovascular events and progression to lower kidney function than the patient in case 1. He also needs to be screened for undiagnosed hypertension and underlying glomerular disease.

■ REFERRAL TO (AND COLLABORATION WITH) A NEPHROLOGIST

Effective co-management with a nephrologist is essential for the overall health of the patient with chronic kidney disease, as well as slowing the progression to end-stage renal disease. Exactly when and to what extent the care of a patient with chronic kidney disease should be transferred to a nephrologist and the comfort level of the primary care provider. When the referral does occur, effective communication between providers and a mutual understanding of the goals of care (eg, the blood pressure target) are essential to optimize patient care. ■

■ REFERENCES

1. 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):S1–S266.
2. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; 130:461–470.
3. Levey AS, Coresh J, Greene T, et al; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the Modification of Diet in Renal Disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; 145:247–254.
4. Levey AS. Measurement of renal function in chronic renal disease. *Kidney Int* 1990; 38:167–184.
5. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 2006; 354:2473–2483.

Screening includes the estimated GFR and urinalysis for blood and protein

6. **Toto RD.** Conventional measurement of renal function utilizing serum creatinine, creatinine clearance, inulin and para-aminohippuric acid clearance. *Curr Opin Nephrol Hypertens* 1995; 4:505–509.
7. **Hilbrands LB, Artz MA, Wetzels JF, Koene RA.** Cimetidine improves the reliability of creatinine as a marker of glomerular filtration. *Kidney Int* 1991; 40:1171–1176.
8. **Hottelart C, El Esper N, Rose F, Achard JM, Fournier A.** Fenofibrate increases creatininemia by increasing metabolic production of creatinine. *Nephron* 2002; 92:536–541.
9. **Rolin HA III, Hall PM.** Evaluation of glomerular filtration rate and renal plasma flow. In: Jacobson HR, Striker GE, Klahr S, editors. *The Principles and Practice of Nephrology*, 2nd ed. St. Louis: Mosby-Year Book, Inc., 1995: 8–13.
10. **Cockcroft DW, Gault MH.** Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31–41.
11. **Stevens LA, Coresh J, Feldman HI, et al.** Evaluation of the Modification of Diet in Renal Disease study equation in a large diverse population. *J Am Soc Nephrol* 2007; 18:2749–2757.
12. **Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration).** A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150:604–612.
13. **Vassalotti JA, Stevens LA, Levey AS.** Testing for chronic kidney disease: a position statement from the National Kidney Foundation. *Am J Kidney Dis* 2007; 50:169–180.
14. **Hemmelgarn BR, Manns BJ, Lloyd A, et al; Alberta Kidney Disease Network.** Relation between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010; 303:423–429.
15. **Glassock RJ, Winearls C.** Screening for CKD with eGFR: doubts and dangers. *Clin J Am Soc Nephrol* 2008; 3:1563–1568.
16. **Poggio ED, Rule AD.** A critical evaluation of chronic kidney disease—should isolated reduced estimated glomerular filtration rate be considered a ‘disease’? *Nephrol Dial Transplant* 2009; 24:698–700.
17. **Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY.** Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; 351:1296–1305.
18. **Glassock RJ.** Referrals for chronic kidney disease: real problem or nuisance? *JAMA* 2010; 303:1201–1203.
19. **Tonelli M, Muntner P, Lloyd A, et al, for the Alberta Kidney Disease Network.** Using proteinuria and estimated glomerular filtration rate to classify risk in patients with chronic kidney disease. A cohort study. *Ann Intern Med* 2011; 154:12–21.
20. **Lindeman RD, Tobin JD, Shock NW.** Association between blood pressure and the rate of decline in renal function with age. *Kidney Int* 1984; 26:861–868.

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