Estimating the glomerular filtration rate

Dos and don'ts for assessing kidney function

CHRONIC KIDNEY DISEASE SERIES

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PREVIEW

Early detection and management of chronic kidney disease (CKD) hold the promise of decreasing the risk of complications of CKD and preventing kidney failure. One of the challenges, however, is that the early stages of CKD are silent and are detectable only through laboratory analyses. Glomerular filtration rate (GFR) remains the most accurate index of kidney function—and is thus key to early management of the disease. In this article, Drs Manjunath, Sarnak, and Levey offer information on how best to estimate GFR and outline limitations of using prediction equations.

Accurate assessment of the level of kidney function is key to the identification and management of CKD. The early stages of CKD are silent and are detected only by laboratory investigation. Kidney function declines progressively over time in most kidney diseases, leading to complications such as hypertension, anemia, malnutrition, bone disease, neuropathy, decreased functioning and well-being and, eventually, kidney failure. Recent clinical trials have shown that, even when kidney disease cannot be cured, the rate of decline can be slowed by routine clinical interventions such as strict glucose control in diabetes, strict blood pressure control, use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers and, possibly, dietary protein restriction. Therefore, early detection and management of CKD hold the promise of decreasing the risk of complications of CKD and kidney failure.

In the later stages of CKD, accurate determination of the level of kidney function is also essential for optimal dosing of medications, interpretation of signs and symptoms that may be caused by complications of CKD, and assessment of the need for kidney replacement therapy.

Third in a series of articles on chronic kidney disease, coordinated by the National Kidney Foundation and Garabed Eknoyan, MD, professor of medicine, department of medicine, Baylor College of Medicine, Houston.

GFR as an index of kidney function

The guidelines of the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative classify stages of CKD according to the level of estimated GFR, which is considered the best index of kidney function in both health and disease.[1] GFR is a direct measurement of kidney function[2] and is reduced before the onset of symptoms of kidney failure.[3] A decrease in GFR correlates with the pathologic severity of kidney disease.[4,5] Replacement therapy with dialysis or transplantation becomes necessary when the GFR decreases below 15 mL/min/1.73 m^2.

The level of GFR is the product of the single nephron filtration rate multiplied by the number of functioning nephrons in both kidneys and can be denoted as

$$(1)\ GFR = N \times SNGFR$$

where SNGFR is the GFR of a single nephron and N is the total number of nephrons in both kidneys. GFR can be decreased either because of reduced nephron number (as in CKD) or because of reduction in SNGFR (caused by physiologic or pharmacologic alterations in glomerular hemodynamics). Factors that affect GFR are listed in table 1.[6]

It is important to recognize that the level of GFR can be

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Table 1. Factors affecting GFR

- Kidney disease
- Pregnancy
- Reduced kidney perfusion
- Marked increase or deficit of extracellular fluid volume
- Nonsteroidal anti-inflammatory drug use
- Acute protein load and habitual protein intake
- Blood glucose control (in diabetic patients)
- Level of arterial blood pressure and class of antihypertensive agents used

GFR, glomerular filtration rate.

Adapted from Levey.[6]

insensitive in detecting loss of nephron number because of compensatory increases in SNGFR secondary to increased glomerular capillary pressure or glomerular hypertrophy. A good example of this phenomenon occurs with early diabetic kidney disease, in which hyperfiltration actually leads to an increase in SNGFR and therefore in GFR.

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Filtration markers

GFR is estimated from the urinary clearance of an ideal filtration marker, defined by

$$(2)\ C_i = U_i V/P_i$$

where C_i is the clearance of the ideal filtration marker (i), U_i is the urinary concentration of i, V is the urine flow rate, and P_i is the average plasma concentration of i during the time interval of urine collection. If substance i is freely filtered across the capillary wall and neither secreted nor reabsorbed, then C_i = GFR.

Inulin fulfills the criteria as an ideal filtration marker, and its urinary clearance has long been considered the "gold standard" in measuring GFR.[7] Normal values for inulin clearance in young men and women are approximately 130 and 125 mL/min/1.73 m^2, respectively. The values decline with age by approximately 10 mL/min/1.73 m^2 per decade after 30 to 40 years of age.

Although inulin is considered to be the ideal filtration marker, its availability is limited and the protocols for measurement of inulin clearance are inconvenient. Alternative clearance methods that use exogenous filtration markers, such as iothalamate sodium I 125 and technetium Tc 99m DPTA, are simpler and have been used in clinical trials.[8] Nonetheless, they are inconvenient and expensive because of the use of radioactive material, the requirement that multiple blood and urine measurements be taken over 3 to 4 hours, and the need for trained personnel to perform the procedure.

Clearance of endogenous filtration markers, such as creatinine (cr) and urea, has also been used to assess GFR.[9,10] Specifically,

$$(3)\ C_{cr} = U_{cr} V/P_{cr}$$

where C_{cr} is the clearance of creatinine, U_{cr} is the urinary concentration of creatinine, and P_{cr} is the serum creatinine; and

$$(4)\ C_{urea} = U_{urea}/P_{urea}$$

where C_{urea} is the clearance of urea, U_{urea} is the urinary excretion of urea, and P_{urea} is the average plasma concentration of urea.

In clinical circumstances, both methods are limited by errors that can occur when a timed urine sample is collected. Urea excretion varies widely according to protein intake, but creatinine excretion is relatively constant over time. Therefore, serum creatinine varies reciprocally with creatinine clearance (equation 3).[11]

To overcome the inconvenience and inaccuracy of timed urine collections, most clinicians

have estimated the level of GFR from the serum creatinine concentration, defined as equation 5:

(5) $GFR \propto 1/P_{cr}$

Serum creatinine as an index of GFR

Use of the serum creatinine level as an index of GFR rests on three important assumptions: (1) creatinine is an ideal filtration marker whose clearance approximates GFR, (2) creatinine excretion rate is constant among persons and over time, and (3) measurement of serum creatinine is accurate and reproducible across clinical laboratories. Although serum creatinine concentration can provide a rough index of the level of GFR, none of these assumptions is strictly true, and numerous factors can lead to errors in estimation of the level of GFR from the serum creatinine concentration (table 2).

Table 2. Factors that affect serum creatinine concentration

Factor	Effect on serum creatinine	Mechanism (comment)
Kidney disease	Increase	Decreased GFR (increase is blunted by increased tubular secretion of creatinine and by reduced creatinine generation)
Reduced muscle mass	Decrease	Reduced creatinine generation (common in children, women, and older and malnourished patients)
Ingestion of cooked meat	Increase	Transient increase in creatinine generation (increase may be blunted by transient increase in GFR)
Malnutrition	Decrease	Reduced creatinine generation (caused by reduced muscle mass and reduced meat intake)
Use of cimetidine (Tagamet), trimethoprim (Proloprim, Trimpex)	Increase	Inhibition of tubular creatinine secretion
Use of flucytosine (Ancobon), some cephalosporins	Increase	Positive interference with iminohydrolase and picric acid assays for creatinine, respectively
Ketoacidosis	Increase	Positive interference with picric acid assay for creatinine

GFR, glomerular filtration rate.

Adapted from Levey.[6]

Creatinine excretion by the kidney

Creatinine is freely filtered by the glomerulus, but it is also secreted by the proximal tubule. Hence, the amount of creatinine excreted in the urine is the composite of both the filtered and secreted creatinine, which can be represented by

(6) $U_{cr} \times V = GFR \times P_{cr} + Ts_{cr}$

where Ts_{cr} is the rate of tubular creatinine secretion. Dividing by P_{cr} and using information from equation 3,

(7) $C_{cr} = GFR + C_{Ts_{cr}}$

where $C_{Ts_{cr}}$ is the clearance of creatinine caused by tubular secretion. Thus creatinine clearance systematically overestimates GFR. This overestimation is about 10% to 40% in healthy persons but is greater and more unpredictable in patients with CKD (figure 1a).[12,13] Factors other than the level of GFR can also

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influence creatinine secretion. For example, creatinine secretion is inhibited by use of some common medications (table 2), such as cimetidine (Tagamet) and trimethoprim (Proloprim, Trimpex).

Creatinine metabolism

Urinary creatinine excretion represents the difference between creatinine generation in the body (G_{cr}) and extrarenal creatinine elimination (E_{cr}):

$$(8)\ U_{cr} \times V = G_{cr} - E_{cr}$$

Substituting into equation 6 and rearranging for P_{cr} yield the following equation:

$$(9)\ P_{cr} = (G_{cr} - E_{cr} - Ts_{cr})/GFR$$

It can therefore be inferred that the relationship between serum creatinine and GFR is affected by the generation and extrarenal excretion of creatinine, as well as the filtration and secretion of creatinine by the kidney.

Creatinine is mainly derived from the metabolism of creatine in muscle, and its generation is proportional to total muscle mass. As a result, mean creatinine generation is higher in men than in women, in younger than in older persons, and in blacks than in whites. This leads to differences in serum creatinine concentration according to sex, age, and race, even after adjusting for GFR. Muscle wasting is also associated with reduced creatinine generation, and in malnourished patients with CKD, it produces a lower serum creatinine value than expected for the level of GFR. Creatinine generation is also affected to a certain extent by consumption of cooked meat, because the cooking process converts a variable portion of creatine to creatinine. Therefore, serum creatinine level is lower than expected for the level of GFR in patients following a low-protein diet.

Although extrarenal creatinine excretion is minimal in people with normal kidney function, it is increased in patients with CKD because of the degradation of creatinine by bacterial overgrowth in the small bowel. As much as two thirds of total daily creatinine excretion can occur by extrarenal creatinine elimination in patients with severely reduced kidney function. As a consequence of all these factors, urinary creatinine excretion is lower in patients with CKD, which leads to systematic overestimation of GFR from serum creatinine. The concentration of serum creatinine can remain less than 2.0 mg/dL, despite decreases in GFR levels to as low as 15 to 20 mL/min/1.73 m² (figure 1b).[13]

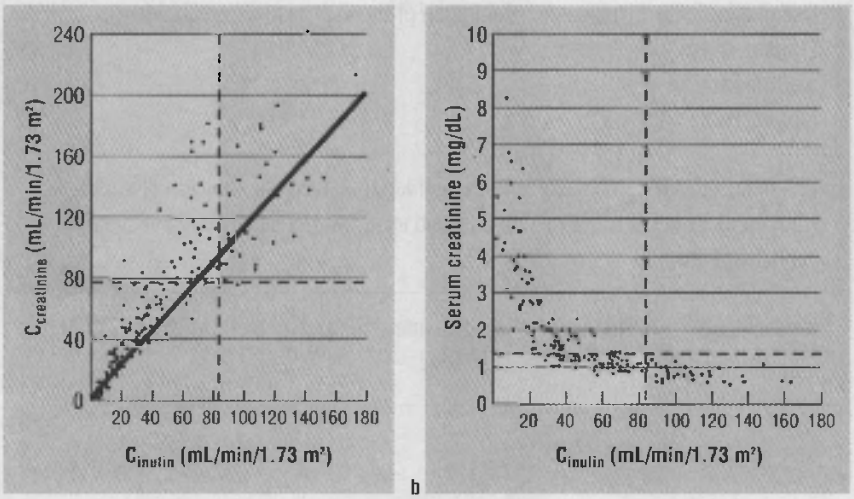

Figure 1a. Relationship of creatinine clearance to glomerular filtration rate (GFR) (inulin clearance) in patients with kidney disease. The horizontal line indicates the lower limit of normal for creatinine clearance, and the vertical line indicates the lower limit of normal for GFR. The diagonal line is the line of identity; the shaded area represents the proportion of patients in whom the level of creatinine clearance is normal despite reduced GFR. b. Relationship of serum creatinine to GFR (inulin clearance) in patients with kidney disease. The horizontal line indicates the upper limit of normal for serum creatinine, and the vertical line indicates the lower limit of normal for GFR. The shaded area represents the proportion of patients in whom serum creatinine is normal despite reduced GFR.

Adapted from Levey et al.[13] Originally published in Shemesh et al[2] and reprinted with permission.

Creatinine measurement

The normal level for serum creatinine concentration is approximately 1.0 mg/dL. The traditional assay for measurement of creatinine is the alkaline picrate method, which detects noncreatinine chromogens in serum (approximately 0.2 mg/dL), as well as creatinine.[14] Urine does not contain noncreatinine chromogens, nor are these compounds retained in CKD. Thus, in the past, measured creatinine clearance has systematically underestimated true creatinine clearance. By coincidence, the difference between measured and true creatinine clearance is similar in magnitude to the clearance of creatinine caused by tubular secretion. Hence, measured creatinine clearance has historically approximated the level of GFR.

Modern autoanalyzers use serum creatinine assays with less interference by noncreatinine chromogens (eg, kinetic alkaline picrate method or enzymatic methods, such as the iminohydrolase method) than in the past. Consequently, normal levels of serum creatinine are now lower, resulting in higher values for measured creatinine clearance and overestimation of GFR.[15] To minimize this overestimation of GFR, autoanalyzer manufacturers and clinical laboratories deliberately calibrate the instruments to report higher serum creatinine values. However, the calibration is not standardized, leading to variation within and across laboratories.[16] This variation is proportionately greater at low serum creatinine values than at high values.

Because clinical laboratories have information on patient demographics and serum creatinine, they should report estimated GFR along with serum creatinine concentration.

In addition to noncreatinine chromogens, other substances may also interfere with serum creatinine assays. These substances, including ketones and some medications, may lead to spurious elevation in serum creatinine concentration and underestimation of GFR (table 2).

Equations to estimate GFR

Numerous formulas have been developed to estimate GFR or creatinine clearance from serum creatinine and other variables. One widely used formula to predict creatinine clearance was proposed by Cockcroft and Gault[17] (table 3). The Cockcroft-Gault equation predicts creatinine clearance (mL/min) from serum creatinine, age, and weight. Height must also be measured to compute body surface area and express the result in conventional units (mL/min per 1.73 m^2). The Cockcroft-Gault equation was derived from an investigation of 249 men with creatinine in a steady state; the subsequent companion equation for women was based on their 15% lower muscle mass. In one study of 394 subjects (208 men and 186 women),[18] the correlation between estimated creatinine clearance and measured GFR was excellent (R^2 = 84%).

More recently, an equation was developed to predict GFR using data from 1,628 patients enrolled in the baseline period of the Modification of Diet in Renal Disease (MDRD) study[19] (table 3). The correlation of GFR predicted from the "six-variable equation" with measured GFR was outstanding (R^2 = 90.3%); the correlation using the "four-variable equation" was almost as high (R^2 = 89.2%).[20] By contrast, creatinine clearance measured by 24-hour urine collections or predicted by the Cockcroft-Gault equation overestimated GFR by 19% and 16%, respectively.[19] Even after researchers adjusted for the systematic overestimation of GFR by creatinine clearance, the correlation of measured creatinine clearance and creatinine clearance computed using the Cockcroft-Gault equation was

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Table 3. Equations that predict kidney function

Investigators	Estimates	Formula	Explanation
Cockcroft and Gault, 1976[17]	C_{cr} (mL/min)	$C_{cr} = \frac{(140 - \text{age}) \times \text{TBW} \times F}{72 \times S_{cr}}$	F = 1 for male; F = 0.85 for female
Levey and colleagues, 1999[19]	GFR (mL/min/1.73 m^2)	GFR = $170 \times (S_{cr})^{-0.999} \times (\text{age, yr})^{-0.176}$ $\times$ 0.762 (if patient is female) $\times$ 1.18 (if patient is black) $\times$ $(\text{SUN})^{-0.17} \times (\text{alb})^{+0.318}$	6-variable MDRD study formula
Levey and colleagues, 2000[20]	GFR (mL/min/1.73 m^2)	GFR = $186.3 \times (S_{cr})^{-1.154} \times (\text{age, yr})^{-0.203}$ $\times$ 1.212 (if patient is black) $\times$ 0.742 (if patient is female)	Simplified 4-variable MDRD study formula

Alb, serum albumin in g/dL; C_{cr}, creatinine clearance; F, factor; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; S_{cr}, serum creatinine in mg/dL; SUN, serum urea nitrogen in mg/dL; TBW, total body weight in kg.

Information from Cockcroft and Gault,[17] Levey et al,[19] and Levey et al.[20]

lower (R^2 = 86.6% and 84.2%, respectively).

Thus both the Cockcroft-Gault and MDRD study equations provide reasonably accurate estimates of GFR. In patients with CKD, the MDRD study equation appears to provide a more accurate and precise estimate of GFR than either the Cockcroft-Gault equation or measured creatinine clearance.

The limitations of GFR equations

Using prediction equations to estimate GFR has limitations. First, the performance of prediction equations in clinical practice is not usually as good as in the study in which they were developed. Although both the Cockcroft-Gault equation and the MDRD study equation have been validated in other studies, they should be used with caution in subgroups of the population that were not included in the development or validation samples, such as children, the elderly, pregnant women, and patients with reduced muscle mass, liver disease, or malnutrition.

Additionally, all prediction equations based on serum creatinine concentration can be misleading in patients who are not in a steady state of creatinine balance (eg, patients with acute kidney failure). In principle, measured GFR will be lower than predicted if serum creatinine is rising, and it will be higher than predicted if serum creatinine is falling. In these cases, the best method for accurately estimating kidney function is to measure creatinine clearance or clearance of the ideal filtration markers.

Factors that interfere with tubular creatinine secretion or creatinine measurement will cause errors in estimation of GFR. Also, variation in calibration of autoanalyzers will cause systematic error in GFR estimates. It would be desirable to, in the future, standardize calibration of instruments according to an international standard for serum creatinine.

Busy physicians are not likely to compute estimated GFR from laboratory reports of serum creatinine measurements. Because clinical laboratories have information on patient demographics and serum creatinine, they should

report estimated GFR along with serum creatinine concentration. For ease in interpretation, the report could also provide the reference range for GFR, including variations according to age and sex (table 4),[21-24] as well as the Kidney Disease Outcomes Quality Initiative's definition and classification of stages of CKD according to GFR level (table 5). These inclusions would serve to improve decision making in patient care.

Decision making in CKD is based on various factors in addition to the level of GFR. For example, the decision to initiate kidney replacement therapy is based on a combination of clinical signs and symptoms, assessment of the level of kidney function, and dietary protein intake.[25]

In the future, other endogenous filtration markers, such as cystatin C,[26] may prove to be more accurate indices of the level of GFR than serum creatinine. If so, prediction equations should be developed to estimate GFR from the level of cystatin or other filtration markers.

Summary

The National Kidney Foundation's guidelines for CKD make the following recommendations about assessment of kidney function.

Estimates of GFR are the best overall indices of the level of kidney function.

- The level of GFR should be

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Table 4. Suggested reference values for GFR by age and sex

Age (yr)	Men* GFR (mL/min/1.73 m²)				Women† GFR (mL/min/1.73 m²)			
	Mean	SD	Mean +/- 2SD		Mean	SD	Mean +/- 2SD	
20-29	128	25.6	77	179	118	23.6	71	165
30-39	116	23.2	70	162	107	21.3	64	149
40-49	105	21.0	63	147	97	19.3	58	135
50-59	93	18.6	56	130	86	17.1	51	120
60-69	81	16.2	49	113	75	14.9	45	104
70-79	70	14.0	42	98	64	12.9	39	90
80-89	58	11.6	35	81	53	10.7	32	75

GFR, glomerular filtration rate.

*Values for GFR in normal men by age[21] and assuming a coefficient of variation (SD/mean) of 20% at all ages. Mean GFR for age categories in men based on linear regression.[22] Regression equation is GFR = −1.163 × age (in yr) + 157.

†Assumes that values for women are 8% lower at all ages than for men.[23,24]

Table 5. Definition and stages of chronic kidney disease*

GFR (mL/min/1.73 m²)	With kidney damage†		Without kidney damage	
	With HBP‡	Without HBP	With HBP	Without HBP
≥90	1	1	HBP	Normal
60-89	2	2	HBP with ↓ GFR	↓ GFR§
30-59	3	3	3	3
15-29	4	4	4	4
<15 or dialysis	5	5	5	5

GFR, glomerular filtration rate; HBP, high blood pressure.

*Shaded area represents chronic kidney disease (CKD); numbers represent stages of CKD.

†Markers of kidney damage include pathologic abnormalities or abnormalities in blood or urine tests or imaging studies.

‡High blood pressure is defined as ≥140/90 mm Hg in adults and >90th percentile for height and gender in children.

§May be normal for age.

Information from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative CKD guidelines, current as of September 2001.

estimated from prediction equations that take into account the serum creatinine concentration and some or all of the following variables: age, gender, race, and body size. In adults, the MDRD study and Cockcroft-Gault equations provide useful estimates of GFR. In children, the Schwartz and Counahan-Barratt equations are useful.

- The serum creatinine concentration should not be used alone to assess the level of kidney function.
- Clinical laboratories should report an estimate of GFR using a prediction equation, in addition to reporting the creatinine measurements.
- Autoanalyzer manufacturers and clinical laboratories should calibrate serum creatinine assays using an international standard.
- Measurement of creatinine clearance using timed (eg, 24-hour) urine collections does not improve the estimate of GFR over that provided by prediction equations. A 24-hour urine sample provides useful information for estimation of GFR in individuals with exceptional dietary intake (vegetarian diet, use of creatine supplements) or muscle mass (amputation, malnutrition, muscle wasting). It is also useful for assessment of diet and nutritional status and need to start dialysis. **PGM**

Earn credit in this issue. See CME Quiz, page 11.

Information pertaining to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) CKD guidelines is current as of September 2001. The final recommendations will be published in January 2002 in a supplement to the *American Journal of Kidney Diseases*.

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