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Assessing Kidney Function — Measured and Estimated Glomerular Filtration Rate

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MANY ORGANIZATIONS RECOMMEND THE USE OF EQUATIONS THAT estimate the glomerular filtration rate (GFR) to facilitate the detection, evaluation, and management of chronic kidney disease.[1-11] Indeed, many clinical laboratories already report estimated GFR values whenever the serum creatinine level is measured. In this review, we discuss the strengths and weaknesses of current methods of measuring and estimating GFR as applied to chronic kidney disease.

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CHRONIC KIDNEY DISEASE

Chronic kidney disease has recently been recognized as a public health problem; it is estimated that by 2030, more than 2 million people in the United States will need dialysis or transplantation for kidney failure.[12] Currently, approximately 19 million adults in the United States are in the early stages of the disease,[13] defined by either a GFR of less than 60 ml per minute per 1.73 m² of body-surface area or the presence of kidney damage, regardless of the cause, for three or more months[2,14,15] (Table 1 and Fig. 1). Risk factors for chronic kidney disease include an age of more than 60 years, hypertension, diabetes, cardiovascular disease, and a family history of the disease. Recommendations for evaluating people at increased risk are to measure urine albumin to assess kidney damage and to estimate the GFR with an equation based on the level of serum creatinine.[2,5,10,11,16]

Once chronic kidney disease is detected, identification of the cause, coexisting conditions, and stage (Table 1) is essential for further evaluation and management. An estimated GFR of less than 60 ml per minute per 1.73 m² is associated with a graded increase in the risk of each of the major adverse outcomes of chronic kidney disease, which are impaired kidney function, progression to kidney failure, and premature death caused by cardiovascular disease (Fig. 2).[2,11,17-19] The large number of patients who have chronic kidney disease, together with the number of people at increased risk for it, requires primary care providers, as well as specialists in areas other than nephrology, to increase their familiarity with the use of GFR estimates.

MEASUREMENT OF GFR WITH EXOGENOUS FILTRATION MARKERS

GFR is accepted as the best overall measure of kidney function.[15,20] Normal values, which are related to age, sex, and body size, are approximately 130 ml per minute per 1.73 m² in young men and 120 ml per minute per 1.73 m² in young women. Mean values decline as persons age (Fig. 1).[15]

Table 1. Stages of Chronic Kidney Disease (CKD), Prevalence in the United States in 2000, and Stage-Specific Recommendations for Detection, Evaluation, and Management.

Stage of CKD	Description	GFR	Detection, Evaluation, and Management*	Prevalence†	
				%	No. of Cases (95% CI)
		ml/min/1.73 m²			*millions*
1	Kidney damage with normal or increased GFR	>90	Diagnosis and treatment Treatment of coexisting conditions Slowing progression Risk reduction for cardiovascular disease	2.8	5.6 (4.0–7.2)
2	Kidney damage with mild decrease in GFR	60–89	Estimation of progression	2.8	5.7 (4.2–7.2)
3	Moderate decrease in GFR	30–59	Evaluation and treatment of complications	3.7	7.4 (6.0–8.9)
4	Severe decrease in GFR	15–29	Referral to nephrologist and consideration for kidney replacement therapy	0.1	0.30 (0.02–0.5)
5	Kidney failure	<15	Replacement (if uremia present)	0.2	0.30‡

* The importance of the GFR is cumulative in that recommended care at each stage of CKD includes care for less severe stages. Adapted from the Kidney Disease Outcome Quality Initiative of the National Kidney Foundation.[2]

† Kidney damage is defined as persistent albuminuria on two occasions. Estimates are similar to those from the Third National Health and Nutrition Evaluation Survey (1988 to 1994), which are derived from a larger number of subjects and are therefore more precise.[13] CI denotes confidence interval.

‡ Data on the prevalence of stage 5 are from the U.S. Renal Data System for the number of patients receiving dialysis therapy. This value is an underestimate, since it does not include the additional unknown number with kidney failure who are not receiving treatment.[2,14]

GFR is measured as the urinary or plasma clearance of an ideal filtration marker such as inulin or of alternative exogenous markers such as iothalamate, EDTA, diethylene triamine pentaacetic acid, and iohexol. Measuring clearance with the use of exogenous markers is complex, expensive, and difficult to do in routine clinical practice.[21] Furthermore, research studies have reported a measurement error of 5 to 20 percent (variation within a single clearance procedure or between clearance procedures on different days).[22-25] The variation is greater in the higher ranges of GFR on the absolute scale.[22]

ESTIMATION OF GFR WITH ENDOGENOUS FILTRATION MARKERS

Urinary clearance of an endogenous filtration marker such as creatinine can be computed from a timed urine collection (for example, a 24-hour urine collection) and blood sampling during the collection period without the need for the administration of an exogenous marker. Nonetheless, timed urinary collections are cumbersome and susceptible to error, and 24-hour urine collections for the measurement of creatinine clearance are no longer recommended routinely to estimate the level of kidney function.

In the steady state, the serum level of an endogenous marker is related to the reciprocal of the level of GFR and can be used to estimate the GFR without a urine collection. The serum level of endogenous filtration markers can also be affected by factors other than the GFR, including tubular secretion or reabsorption, generation, and extrarenal elimination of the endogenous filtration marker.

CREATININE

Creatinine is an amino acid derivative with a molecular mass of 113 D that is freely filtered by the glomerulus. Many studies support the similarity of creatinine clearance to GFR and its reciprocal relationship with the serum creatinine level.[26,27] Creatinine is secreted by proximal tubular cells as well as filtered by the glomerulus; thus, the creatinine clearance exceeds the GFR. Tubular secretion of creatinine varies among and within individual persons, especially in those with a mild-to-moderate reduction in the GFR.[28] Some drugs, including trimethoprim and cimetidine, inhibit creatinine secretion, thereby reducing creatinine

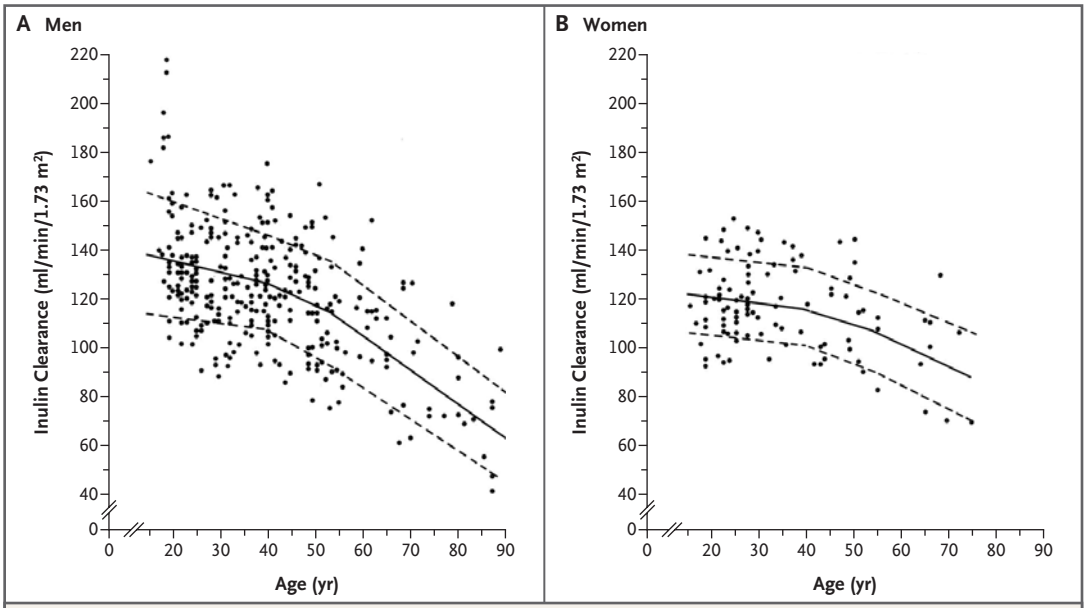

Figure 1. Normal Values for GFR in Men and Women.

Normal values for inulin clearance are shown for men (Panel A) and women (Panel B) of various ages, with the GFR measured as the urinary clearance of inulin. A GFR value of 60 ml per minute per 1.73 m^2 is the threshold for the definition of chronic kidney disease. Solid lines represent the mean value of GFR per decade of age, and dashed lines represent the value 1 SD from the mean value of GFR per decade of age. Adapted from Wesson.[15]

clearance and elevating the serum creatinine level without affecting the GFR.[28,29] The generation of creatinine is determined primarily by muscle mass and dietary intake (Table 2), which probably accounts for the variations in the level of serum creatinine observed among different age, geographic, ethnic, and racial groups.[28,30,31] Extrarenal elimination of creatinine may be increased at low levels of GFR; this increase is mainly related to the degradation of creatinine by intestinal bacteria and can be affected by the use of antibiotics.[26,27] For these reasons, the relationship between the levels of serum creatinine and GFR varies substantially among persons and over time. The use of a single reference range for serum creatinine to distinguish between a normal GFR and an abnormal one can be misleading (Fig. 3).[26-28,32,34]

CYSTATIN C

Cystatin C, a nonglycosylated basic protein with a low molecular mass (13 kD) that is freely filtered by the glomerulus, is currently under investigation as a replacement for serum creatinine in estimating the GFR.[35-40] After filtration, cystatin C is reabsorbed and catabolized by the tubular epithelial cells; only small amounts are excreted in the urine. Consequently, although cystatin C is cleared by the kidneys, its urinary clearance cannot be measured, which makes the study of the factors affecting its clearance and generation difficult.

The generation of cystatin C appears to be less variable from person to person than that of creatinine. However, there is preliminary evidence that serum levels of cystatin C are influenced by corticosteroid use[41] and are related to age, sex, weight, height, smoking status, and the level of C-reactive protein, even after adjustment for creatinine clearance.[42] Other studies show extrarenal elimination of the protein in the presence of high levels of cystatin C.[36,37] Recent investigations suggest that cystatin C may be a better filtration marker than creatinine, especially at higher levels of GFR. However, it is less certain whether the measurement of cystatin C is an improvement over creatinine-based equations for estimating the GFR.[35,36,43-45]

EQUATIONS USED TO ESTIMATE GFR

Estimating equations include variables such as age, sex, race, and body size, in addition to serum creatinine, as surrogates for muscle mass, and therefore, they can overcome some of the limita-

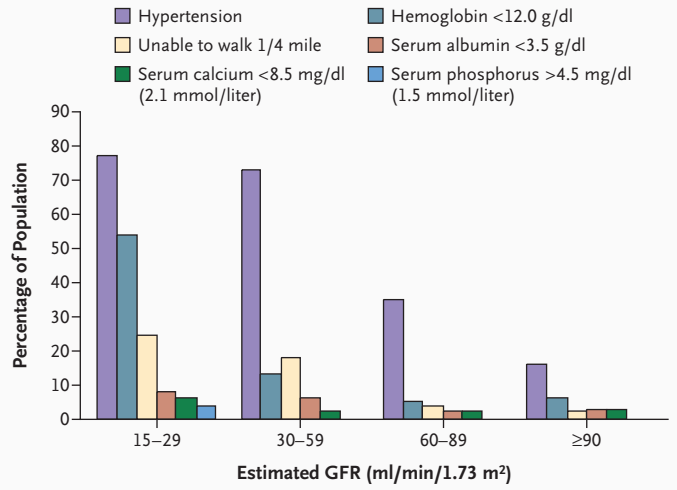

Figure 2. Estimated Prevalence of Complications Related to Chronic Kidney Disease, According to the Estimated GFR in the General Population.

Hypertension was defined as a systolic pressure of 140 mm Hg or higher or a diastolic pressure of 90 mm Hg or higher or the receipt of antihypertensive medication. The study population includes participants in the Third National Health and Nutrition Evaluation Survey (1988 to 1994) who were 20 years of age or older. The GFR is estimated from the four-variable Modification of Diet in Renal Disease study equation with the use of calibrated serum creatinine levels. A total of 10,162 participants with a mean age of 39 years had a GFR greater than 90 ml per minute per 1.73 m^2; 4404 with a mean age of 54 years had a GFR of 60 to 89; 961 with a mean age of 72 years had a GFR of 30 to 59; and 52 with a mean age of 75 years had a GFR of 15 to 29. Adapted from the National Kidney Foundation.[2]

tions of the use of serum creatinine alone. An estimating equation is derived with the use of regression techniques to model the observed relation between the serum level of the marker and the measured GFR in a study population. Estimating equations for GFR have been developed chiefly in study populations consisting predominantly of patients with chronic kidney disease and reduced GFR. Although an equation developed in one population is appropriate for use in that population, evaluation in other populations is necessary to demonstrate the generalizability of the observed relationships. We will focus on two creatinine-based equations that have been extensively studied and widely applied, the Cockcroft–Gault and the Modification of Diet in Renal Disease (MDRD) study equations.[32,33,46,47]

The Cockcroft–Gault formula was developed in 1973 with the data from 249 men with creatinine clearances (C_{cr}) from 30 to 130 ml per minute.[46,48] The estimating equation is $C_{cr} = [(140 - \text{age}) \times \text{weight}/](72 \times S_{cr}) \times 0.85$ (if the subject is female), where C_{cr} is expressed in milliliters per minute, age in years, weight in kilograms, and serum creatinine (S_{cr}) in milligrams per deciliter. It systematically overestimates GFR because of the tubular secretion of creatinine. The values are not adjusted for body-surface area; a comparison with normal values for creatinine clearance requires measurement of height, computation of body-surface area, and adjustment to 1.73 m^2.[49]

The MDRD study equation was developed in 1999 with the use of data from 1628 patients with chronic kidney disease. It estimates GFR adjusted for body-surface area.[32,33] The estimating equation is $GFR = 186 \times (S_{cr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if the subject is female) or $\times 1.212$ (if the subject is black). This equation was reexpressed in 2005 for use with a standardized serum creatinine assay, which yields serum creatinine values that are 5 percent lower[34,47]: $GFR = 175 \times (\text{standardized } S_{cr})^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if the subject is female) or $\times 1.212$ (if the subject is black). GFR is expressed in milliliters per minute per 1.73 m^2, and race is either black or not. The term for race reflects a higher average serum creatinine level in blacks, partly owing to increased muscle mass. In the MDRD study population, 91 percent of the GFR estimates were within 30 percent of the measured values, and this approach was more accurate than either the use of the Cockcroft–Gault equation or the measurement of creatinine clearance, even after adjustment for body-surface area and correction for systematic bias owing to the overestimation of GFR by creatinine clearance (Fig. 4).

To convert the values to SI units (S_{cr} in micromoles per liter), replace 72 in the denominator with 0.84 in the Cockcroft–Gault equation, replace 186 with 32,788 in the original (1999) MDRD study equation,[33] and replace 175 with 30,849 in the reexpressed (2005) MDRD study equation.[47]

EVALUATION OF CURRENT ESTIMATING EQUATIONS

The MDRD study and the Cockcroft–Gault equations have been evaluated in numerous populations, including blacks, whites, and Asians with nondiabetic kidney disease, patients with diabetes and kidney disease, patients with diabetes without kidney disease, kidney-transplant recipients, and potential kidney donors.[50-70] The MDRD study equation is reasonably accurate in nonhospitalized patients known to have chronic kidney disease. In four large studies of persons with chronic kidney disease, the mean difference between estimated and measured GFR ranged from −5.5

to 0.9 ml per minute per 1.73 m².[50-52,54] In some studies, the MDRD study equation has been reported to be more accurate than the Cockcroft–Gault equation,[50-52,54,71] whereas other studies have found that the two yield similar results.[53,63,69,72] The Cockcroft–Gault equation appears to be less accurate than the MDRD study equation in older and obese people.[54,69,71]

Both the MDRD study and the Cockcroft–Gault equations have been reported to be less accurate in populations without chronic kidney disease, such as in young patients with type 1 diabetes without microalbuminuria and in potential kidney donors.[50,52,54,56,57,63] On average, GFR estimates of less than 90 ml per minute per 1.73 m² in this population are lower than the directly measured values; mean differences between GFR estimates from the MDRD study equation and the direct GFR measurement range from –29 to 3.3 ml per minute per 1.73 m².[50,52,54,63,69] This difference may lead to a false positive diagnosis of chronic kidney disease (a GFR of less than 60 ml per minute per 1.73 m²) in persons who do not have the disease but have a mild reduction in GFR. However, despite the potential misclassification, studies in the general population show that an estimated GFR of less than 60 ml per minute per 1.73 m² is associated with an increased risk of adverse outcomes of chronic kidney disease.[11,17,18,73]

There are several possible explanations for reports that higher GFR estimates may be inaccurate (see the Appendix). First, variation among laboratories in calibration of the serum creatinine assay has a larger effect at higher GFR levels and is probably an important reason for the wide variation in the results of published studies.[74-77] Furthermore, the biologic and measurement variability of GFR is greater at higher levels. Finally, the use of an equation developed in a population with chronic kidney disease may be limited in a population without the disease.

USE OF GFR ESTIMATES

GFR estimates appear to provide a substantial improvement over the measurement of serum creatinine alone in the clinical assessment of kidney function. However, proper interpretation of GFR estimates requires attention to their limitations. The following discussion focuses on the application of current estimating equations for selected aspects of the detection, evaluation, and management of chronic kidney disease (Table 1).

Table 2. Factors Affecting Creatinine Generation.*

Factor	Effect on Serum Creatinine
Aging	Decreased
Female sex	Decreased
Race or ethnic group†	
Black	Increased
Hispanic	Decreased
Asian	Decreased
Body habitus	
Muscular	Increased
Amputation	Decreased
Obesity	No change
Chronic illness	
Malnutrition, inflammation, deconditioning (e.g., cancer, severe cardiovascular disease, hospitalized patients)	Decreased
Neuromuscular diseases	Decreased
Diet	
Vegetarian diet	Decreased
Ingestion of cooked meat	Increased

* Variation in muscle mass accounts for the predominant proportion of creatinine generation.
† White race served as the reference group.

DETECTION OF CHRONIC KIDNEY DISEASE

A persistent reduction in the GFR to less than 60 ml per minute per 1.73 m² is defined as chronic kidney disease.[1,2,5] The differing accuracy of current estimating equations in people with and those without the disease may make it difficult to interpret GFR estimates that are near 60 ml per minute per 1.73 m². In this range, the interpretation of GFR estimates depends on the clinical context. Patients with markers of kidney damage such as proteinuria or abnormalities on imaging studies or on kidney biopsy have the disease, even if GFR estimates are 60 ml per minute per 1.73 m² or greater. Patients without markers of kidney damage who have GFR estimates of 60 ml per minute per 1.73 m² or greater are unlikely to have the disease. There is some uncertainty with respect to patients without markers of kidney damage who have GFR estimates just below 60 ml per minute per 1.73 m². Some of these patients may have a measured GFR above 60 ml per minute per 1.73 m² and therefore would not be considered to have chronic kidney disease. Clinical decision making in these cases will depend on other characteris-

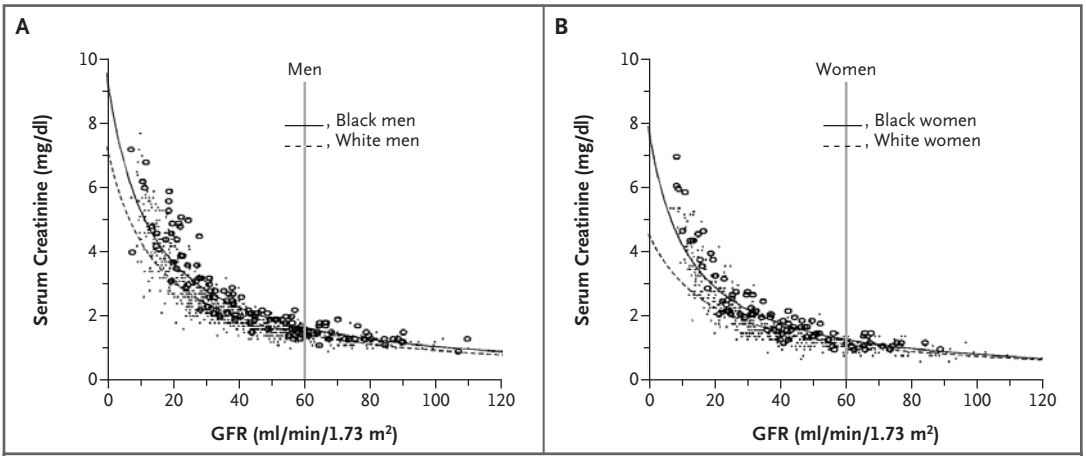

Figure 3. Relationship of Serum Creatinine Level to Measured GFR in the Modification of Diet in Renal Disease Study.
GFR was measured as the urinary clearance of [^{125}I]iothalamate. Serum creatinine was measured with a Beckman Astra CX3 analyzer and a kinetic alkaline picrate assay.[32,33] Regression lines were computed from the relationship of the reciprocal of serum creatinine with GFR. When the GFR was 60 ml per minute per 1.73 m², the 95 percent confidence interval for the serum creatinine level was 1.3 to 1.5 mg per deciliter in white men (measured in 802) and in 1.4 to 1.8 in black men (measured in 113) (left panel) and 1.0 to 1.2 mg per deciliter in white women (measured in 502) and 1.1 to 1.4 mg per deciliter in black women (measured in 84) (right panel). These levels are close to the upper limit of the reference range. Confidence intervals for serum creatinine levels were wider at lower levels of GFR. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. Adapted from Levey et al.[32]

tics of the patients, such as the presence or absence of risk factors for the disease or its complications. Clinicians may decide to defer further evaluation in some patients, but it may be prudent to monitor their estimated GFR more frequently, adjust the dose of medications that are excreted by the kidney, and avoid medications toxic to the kidney.

MONITORING PROGRESSION OF CHRONIC KIDNEY DISEASE

The reciprocal relationship between GFR and serum creatinine levels makes it difficult for clinicians to appreciate the level and rate of change in GFR by simply monitoring serum creatinine levels. For example, in a 50-year-old white man an increase in serum creatinine from 1.0 to 2.0 mg per deciliter (88.4 to 176.8 μmol per liter) reflects a decline in GFR of 46 ml per minute per 1.73 m², but a further increase in the serum creatinine level from 2.0 to 3.0 mg per deciliter (265.2 μmol per liter) reflects a further decline of only 14 ml per minute per 1.73 m².

EVALUATION AND MANAGEMENT OF COMPLICATIONS

Decreased kidney function is associated with many complications, such as hypertension, anemia, malnutrition, bone disease, and a decreased quality of life (Fig. 2).[2] These complications can be treated effectively, especially if detected early.[78-81] Accordingly, testing for complications of this disease has been recommended beginning in patients with stage 3 chronic kidney disease (defined by a GFR of 30 to 59 ml per minute per 1.73 m²).[2]

GFR AND REFERRAL TO NEPHROLOGISTS

Complications related to chronic kidney disease and the risk of severe kidney failure are highest among patients with stage 4 or 5 of the disease.[11,17-19] Late referral to nephrologists before the initiation of dialysis is associated with increased rates of morbidity and mortality.[82-84] Thus, it is important to refer any patient with a GFR estimated to be less than 30 ml per minute per 1.73 m² to a nephrologist for co-management.

MEDICATIONS AND CHRONIC KIDNEY DISEASE

Many medications are excreted by the kidneys and require adjustment in the dose when the GFR is reduced. The Cockcroft–Gault equation has been widely used in pharmacokinetic studies and in the guidance of drug dosing. In most cases, the GFR estimates from the MDRD study and the Cockcroft–Gault equations fall within the same interval for dose adjustment. Nonetheless, until there are more

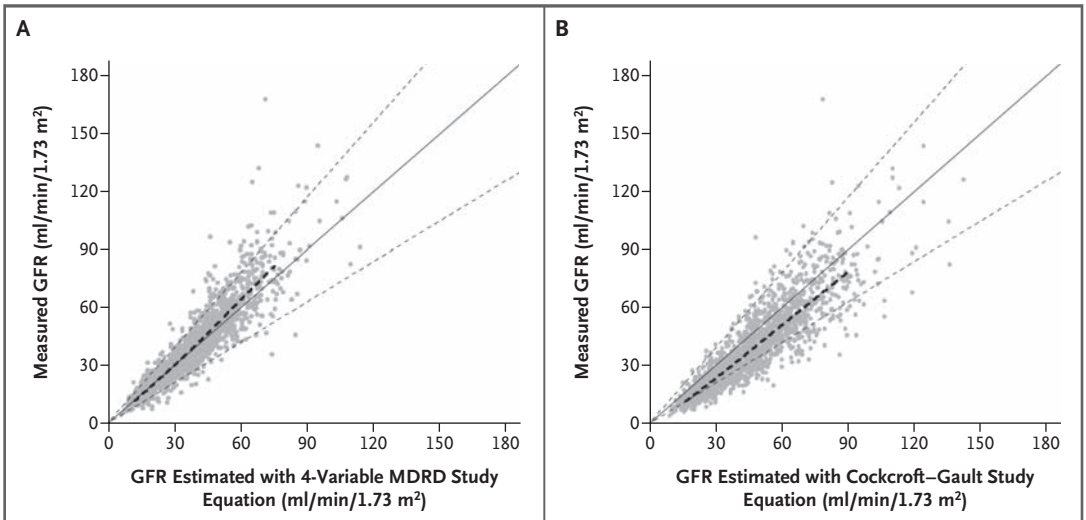

Figure 4. Relation of Estimated GFR to Measured GFR in the Participants in the Modification of Diet in Renal Disease (MDRD) Study.

The GFR was measured in 1628 patients as the urinary clearance of [^{125}I]iothalamate and adjusted for body-surface area. The estimated GFR is expressed with the use of the MDRD study equation (R^2=0.88) (left panel) and the Cockcroft–Gault equation (R^2=0.83) (right panel). Each point represents the baseline measurement. The solid diagonal line represents the line of identity. The bold dashed line represents the fitted line with smoothing-splines function plotted from the 2.5 to the 97.5 percentile of estimated GFR. Thin dashed lines represent the difference of ±30 percent between estimated and measured GFR.[33,47]

data based on the MDRD study equation or other new equations, physicians and pharmacists may choose to continue to use the Cockcroft–Gault equation to adjust drug doses in patients with a decreased estimated GFR. The appropriate adjustment in medication dose for patients who are either very large or very small in size requires the expression of GFR estimates in milliliters per minute, rather than in milliliters per minute per 1.73 m².[49]

Assessment of Risk for Cardiovascular Disease

An estimated GFR below 60 ml per minute per 1.73 m² is a risk factor for both new and recurrent cardiovascular disease in the general population and in people at increased risk for cardiovascular disease.[11,17-19] In these patients, death from cardiovascular disease is more common than progression to kidney failure.[73] Patients with an estimated GFR below 60 ml per minute per 1.73 m² are therefore considered to be in the high-risk group for cardiovascular disease, and they should undergo intensive evaluation and treatment of risk factors for cardiovascular disease.[1,11]

Recent studies suggest that the serum level of cystatin C may be a better predictor of outcomes of cardiovascular disease than GFR estimates based on levels of serum creatinine. It is not known whether the prediction is improved because cystatin C is a better marker of GFR than levels of serum creatinine or because factors apart from GFR that affect the level of cystatin C or creatinine also are related to the risk of cardiovascular disease.[35-45,85-87] For example, many chronic diseases, including cardiovascular disease, are associated with decreased muscle mass and, consequently, lower serum creatinine levels and higher estimated GFR, which would weaken the association of lower estimated GFR and cardiovascular disease. Factors related to higher levels of cystatin C are less well understood, but a reported positive association with C-reactive protein would strengthen the association of a higher level of cystatin C and cardiovascular disease.

When to Consider Clearance Measurements Instead of Estimated GFR

GFR estimates are less accurate in certain circumstances. One such circumstance occurs in people with unusual body habitus or diet (Table 2); for example, a person with substantial muscle wast-

ing may have a lower GFR than suggested by the GFR estimate, even at GFR levels of less than 60 ml per minute per 1.73 m², owing to a low level of creatinine generation. Another circumstance is in patients with rapidly changing kidney function; in these patients, changes in GFR estimates lag behind changes in measured GFR. GFR can be estimated from the rate and magnitude of change in the GFR estimate, analogous to the interpretation of changes in the serum creatinine level in the nonsteady state. The third circumstance involves patients with GFR estimates of 60 ml per minute per 1.73 m² or greater. More accurate estimates may be necessary to evaluate people for kidney donation, administer drugs with marked toxic effects and that are excreted by the kidneys (e.g., high-dose methotrexate), or determine a person's eligibility for research protocols.

Clearance of exogenous filtration markers provides the most accurate measure of GFR and could be used if facilities for administration of the marker and its measurement are available. Creatinine clearance can be measured from a 24-hour urine collection and a single serum sample in the steady state, but the results must be interpreted with caution because of errors in collection of timed urine specimens and because creatinine clearance exceeds GFR. The former source of error might be reduced by repeated measurements and the latter by pretreatment with cimetidine, which partially inhibits creatinine secretion.[88] If cystatin C is shown to be a better endogenous marker of GFR, estimation of GFR from cystatin C might be helpful in some of these circumstances.

GFR Reporting by Clinical Laboratories

Reporting the estimated GFR may improve physicians' recognition of chronic kidney disease.[89] Current recommendations to clinical laboratories take into account the greater inaccuracy of GFR estimates at higher levels.[4] Laboratories should report a specific value of GFR only if the estimated GFR is less than 60 ml per minute per 1.73 m²; higher values should be reported as "GFR is 60 ml per minute per 1.73 m² or more."

CONCLUSIONS

The main limitation of current GFR estimates is the greater inaccuracy in populations without known chronic kidney disease than in those with the disease. Nonetheless, current GFR estimates facilitate detection, evaluation, and management of the disease, and they should result in improved patient care and better clinical outcomes. The reporting of estimated GFR whenever the measurement of serum creatinine is ordered should be coordinated with a campaign to educate physicians, health care organizations, patients, and the public about chronic kidney disease and the interpretation of GFR estimates.

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APPENDIX

MEASURING CREATININE

The alkaline picrate assay is subject to interference by noncreatinine chromogens, causing an overestimation of serum creatinine in normal persons of up to 20 percent.[90] Noncreatinine chromogens are not retained at a reduced GFR; hence, their relative effect is greater at the lower range of levels of serum creatinine. Enzymatic assays do not detect noncreatinine chromogens and yield lower values for serum creatinine. Calibration of serum creatinine assays to adjust for these differences is not standardized across laboratories, leading to substantial variation in reported values among laboratories.[90]

MEASURING CYSTATIN C

Currently, the particle-enhanced nephelometric immunoassay (PENIA) developed for the Dade Behring nephelometers is the most frequently used assay for cystatin C.[40] Studies show variation among assays, and as cystatin C becomes more widely adopted, more assays are likely to become available.

INACCURATE PERFORMANCE OF GFR ESTIMATING EQUATIONS IN POPULATIONS WITHOUT CHRONIC KIDNEY DISEASE

Creatinine Calibration

In a chemistry survey of 5624 clinical laboratories in 2003 by the College of American Pathologists, the peer-group mean bias for serum creatinine ranged from −0.06 to 0.31 mg per deciliter (−5.25 to 27.4 μmol per liter) for a specimen with an assigned value of 0.902 mg per deciliter (79.7 μmol per liter), with 60 percent of the laboratory peer groups having significant bias ($P<0.001$).[90,91] The variation is greater for lower levels of serum creatinine. The calibration of a creatinine assay that differs from the calibration in the laboratory that developed the GFR equation will therefore result in a greater bias for higher levels of GFR.[74-77]

Measurement Error and Biologic Variation in GFR

Reported differences between the estimated and measured GFR reflect, in part, measurement error in the GFR and the normal biologic variation in the GFR, both of which are greater at higher GFR levels. Thus, reported differences would tend to overstate the magnitude of the differences between the estimated and true GFR, especially at higher GFR levels when reported on the raw scale rather than as a percent. Such differences represent a limitation of GFR measurement, rather than of estimating equations as such.

Limitations of Generalizing Equations Developed in Populations with Chronic Kidney Disease

Surrogates for Creatinine Generation

Patients with chronic kidney disease may have lower muscle mass and dietary protein intake than healthy people. Thus, the relationships observed in the populations that were included in the MDRD and Cockcroft–Gault studies may differ from those observed in healthy people, leading to increased errors when estimation equations derived in populations with the disease are applied to healthy people.

Determinants of Variation in Serum Creatinine

The proportional variation in the GFR is larger in populations with the disease (by a factor of approximately 10, from 6 to 60 ml per minute per 1.73 m^2) than in populations without the disease (by a factor of approximately 3, from 60 to 180 ml per minute per 1.73 m^2). As a result, a larger proportion of the variation in serum creatinine levels among patients with the disease is due to a variation in the GFR, not to a variation in the other determinants as compared with healthy people. For example, among patients with the disease, a difference in levels of serum creatinine of 0.8 and 1.2 mg per deciliter (70.7 and 106.1 μmol per liter) probably reflects a difference in the GFR. In contrast, this same difference among healthy people more likely reflects a difference in muscle mass or protein intake, rather than the GFR. When an estimating equation derived in a population with chronic kidney disease is applied to a healthy population, the equation will overstate the strength of the relationship of the GFR with the level of serum creatinine. Thus, in people with an unusually low or high estimated GFR, the measured GFR would tend to fall closer to the normal GFR of the population than the GFR estimates.

Mean Level of GFR

GFR estimates derived through a regression equation will deviate systematically toward the mean of the study population in which the equation was derived (i.e., the phenomenon of regression to the mean). Thus, the mean level of the GFR in healthy people by current estimating equations would be slightly lower than the mean of measured GFR. However, regression to the mean is smaller for estimating equations derived in populations in which the regression model exhibits a high squared correlation (90.3 percent for the MDRD study equation) than it would be for equations derived in populations with lower correlations, as are typically found in the development of equations with a higher or narrower GFR range.

CREATININE STANDARDIZATION

The National Kidney Education Program has initiated a creatinine standardization program to minimize this variation,[34] analogous to the standardization of lipid measurements as the first step of the National Cholesterol Education Program in the 1980s. The results are not expected to be completed until 2008. Until the standardization program is complete, GFR estimates should be computed with the use of the original four-variable MDRD study equation developed in 1999. After standardization is accomplished, estimates computed with the MDRD study equation reexpressed in 2005 will be reasonable.[47]

NEW EQUATIONS TO ESTIMATE GFR

The National Institute of Diabetes and Digestive and Kidney Diseases has funded a research group, Chronic Kidney Disease Epidemiology Collaboration, to develop improved estimating equations for GFR. The group will develop equations from large pooled databases of subjects with formal measurements of GFR, standardized serum creatinine, and cystatin C. New equations will be validated in independent populations to evaluate generalizability. The effect of errors in performance of the equations related to differences in the creatinine assay, GFR-measurement techniques, and population characteristics will be quantified.

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