Chapter 6: Limitations of Various Formulae and Other Ways of Assessing GFR in the Elderly: Is There a Role for Cystatin C?

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GFR is the best index available to assess kidney function in disease and in health in an individual. It is 120 to 130 ml/min per 1.73 m^2 in young, healthy adults, and it decreases by about 0.8 ml/min per 1.73 m^2 per year after 40 yr of age. However, it is important to note that, in the Baltimore Longitudinal Study on Aging, about one third of the patients that were followed did not have a decrease in GFR with aging.

The GFR cannot be measured directly in an individual. Therefore, it is assessed using either exogenous markers or endogenous markers in their steady states as shown in Table 1.

MEASURING GFR USING EXOGENOUS MARKERS

The direct methods in the general population and in elderly persons are riddled with a number of problems (Table 1). Therefore, except in rare situations such as in a prospective kidney donor with borderline GFR for eligibility, these methods are not used in clinical practice.

METHODS OF GFR ESTIMATION USING ENDOGENOUS MARKERS

Serum Creatinine (S_{cr})

GFR estimation based on serum creatinine alone is not an ideal method, especially in elderly persons because it is influenced by a number of variables such as age, gender, muscle mass, diet, and medications that block creatinine's tubular secretion. For example, despite reductions in GFR to <60 ml/min per 1.73 m^2, there may not be a significant increase in creatinine in the elderly persons with decreased muscle mass. On the other hand, if the muscle mass and diet are stable, serum creatinine could be used for monitoring GFR more closely. In general, a change in serum creatinine >15% is likely to indicate a significant fall in GFR in an individual patient rather than being caused by simple biologic and analytical variations. Table 1 shows other limitations of S_{cr}.

Creatinine Clearance

Creatinine clearance as measured from a 24-h urine collection can be used to measure GFR, but it is vital to remember the high likelihood of inaccurate collection, especially in some elderly people with cognitive impairment or the bed bound. It is important, therefore, to check for adequacy of urinary collection before interpretation of clearance. The collection is said to be adequate if the creatinine excretion is 20 to 25 mg/kg per day in a young healthy man and if it is 15 to 20 mg/kg per day in a young healthy woman. In elderly people, adequacy is similarly checked because it is assumed that the muscle mass (and hence creatinine generation) and renal function decline simultaneously with age. Caution must, therefore, be used if this assumption cannot be made in individual instances. If this method is used in the setting of acute renal failure or rapidly changing serum creatinine, it is necessary to measure an average from simultaneous serial serum creatinine values during urine collection. Creatinine clearance systematically overestimates GFR because of tubular secretion of creatinine. The 24-h urine collection for the estimation of GFR has been shown by many studies to not be any more reliable,

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Table 1. Methods of determining GFR and their limitations

Method of Determining GFR		Limitations
Using exogenous markers: GFR can be measured as the urinary or plasma clearance of an ideal filtration marker or of alternative exogenous markers	Ideal filtration marker: inulin clearance	Gold standard: for GFR assessment but is difficult to use in routine practice
	Alternate exogenous markers to inulin: Iohexol ^{51}Cr EDTA ^{125}I-iothalamate, ^{99m}Tc-DTPA	Expensive, less widely available and complex tests
Using endogenous markers: endogenous markers, such as serum creatinine or serum cystatin C can be used to estimate GFR from their serum levels if they are in a steady state.[1] The estimation equations using these endogenous markers adjust to other variables in an attempt to improve accuracy of estimation of GFR from these markers.	Serum creatinine (S_{cr})	Factors influencing S_{cr}:
		(1) Creatinine production: *e.g.*, muscle mass, ingested cooked meat, protein restriction
		(2) creatinine filtration: with age, excretion decreases resulting in underestimation of GFR
		(3) creatinine secretion:
		(i) because of tubular secretion, tends to overestimate GFR by about 10%, increasing significantly as GFR declines
		(ii) cimetidine, trimethoprim inhibit secretion
		(4) Creatinine assay:
		(i) Calibration bias: large variations between laboratories in calibration of the creatinine assays may lead to differences in interpretation of values
		(ii) Factors influencing assay methods-Jaffè reaction based assays-glucose, ketones, bilirubin, cephalosporins and enzymatic method- flucytosine
		(5) Extrarenal elimination may be increased with decreasing GFR (degradation of creatinine by intestinal bacteria)
	Serum cystatin C	See below
	Measured urinary clearance using creatinine	Prone to errors, unpleasant, inconvenient and adequacy of urinary collection needs to ascertained prior to interpretation. The limitations of Scr also applies to this method.
	Serum creatinine-based estimation equations: 1. CG formula 2. MDRD formula	See below
	Estimation of GFR from combined serum creatinine and cystatin C–based equation	Recently published—experience limited

and frequently less reliable, than serum creatinine-based equations. However, in individuals with variation in dietary intake (*e.g.,* vegetarian diet, creatine supplements) or muscle mass (*e.g.,* amputation, malnutrition, muscle wasting), as is seen in many elderly persons, this may be a preferred method because many of these factors are not specifically taken into account in prediction equations. Table 1 shows other limitations.

Creatinine clearance (C_{Cr}) can be calculated if values for urine creatinine concentration (U_{Cr}), urine flow rate (V), and plasma creatinine concentration (P_{Cr}) are known:

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

For the creatinine clearances to be comparable among individuals of different sizes, it is often corrected to that of an average-sized person, which is 1.73 m^2 and expressed as ml/min per 1.73 m^2. If the sizes are extreme, C_{cr} should be corrected for their actual body surface area as follows:

$$\text{Corrected } C_{cr} = (C_{cr} \times 1.73)/\text{Actual body surface area}$$

GFR Estimation by Serum Cystatin C

Cystatin C is an endogenous substance like creatinine but is constitutively produced by all nucleated cells, freely filtered, reabsorbed, and catabolized by the kidney. Most studies have shown that serum cystatin C levels correlate better with GFR than does serum creatinine alone, especially at higher levels of GFR. Its physiologic role is that it is a cysteine proteinase inhibitor with important roles in extracellular proteolysis, immune modulation, and antibacterial and antiviral activities. Some *in vitro* studies have indicated that cystatin C may be affected by some stimuli such as steroids and transforming growth factor *β*. Additionally, cystatin C was thought to be either less influenced or not influenced at all by certain demographic factors such as age, race, gender, or muscle mass compared with serum creatinine in reflecting GFR until recently. There are now emerging data showing that it is, in fact, influenced by some of these factors. For instance, a recent study, although not necessarily focusing entirely on elderly people, with subjects with a mean age of 52 yr, concluded that cystatin C was 9% lower in women and 6% higher in blacks for a given GFR[2,3]. Similarly, another recent study that reported population distributions of cystatin C in the United States using sera samples from the Third National Health and Nutritional Examination Survey noted that abnormal cystatin C was more prevalent with increasing age from 1% in the 20- to 40-yr-old group to >50% in persons over age 80 yr of age within each demographic subgroup.[3,4] However, the definition of abnormal cystatin C levels was chosen as the 99th percentile distribution among 20 to 40 yr olds, without hypertension or diabetics. Although it is plausible that cystatin C rises with age for the reason that there is, in general, a decline in kidney function as noted after the age of 40 yr, it is equally plausible that it could be elevated in the elderly, at least partly, for reasons that are related to the primary function of cystatin C, for example, immunity-related reasons, and not for reasons related to the kidney.

Tables 2 and 3 show factors likely to influence cystatin C levels and limitations, respectively.[5]

GFR ESTIMATION FROM SERUM CREATININE-BASED EQUATIONS

The two most commonly used equations to estimate GFR are serum creatinine based: Cockcroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) equations. Essentially, compared with serum creatinine, these equations increase the accuracy of estimated GFR (eGFR) to the measured GFR by accounting for variables such as age and weight in the former equation and age, gender, and race in the latter one.

CG Equation

This is one of the most widely used equations, even among elderly people, although it was originally derived from mostly younger subjects, with only a 4% female representation.[6] The main intention of the equation was to predict creatinine clearance instead of GFR, and hence, it was validated against measured creatinine clearance. Creatinine clearance, as we know, overestimates GFR; therefore, the CG equation that estimates creatinine clearance should also overestimate GFR. However, studies indicate that it actually underestimates GFR in the elderly, especially at higher GFRs. According to one study, for instance, both the MDRD and CG equations underestimated GFR in hospitalized older individuals, but CG did so more than MDRD.[7] Nevertheless, most of the estimated values using this equation (a median of 75%) were within 30% of measured GFR, which was acceptable for good clinical decision making and superior to serum creatinine alone. Table 4 shows additional limitations.

The CG equation is as follows:

For men: *CrCl* (ml/min) = {[(140 − Age in(yr)]

$$\times \text{Weight(kg)}\}/\text{SCr(mg/dl)} \times 72$$

where CrCl is creatinine clearance and SCr is serum creatinine.

For women, the above equation should be multiplied by 0.85.

In cases of persons of extreme weights, some have used lean body mass, whereas others have used correction of the eCrCl to average body surface area.

Table 2. Factors considered to influence cystatin c levels

Serum Cystatin C Level	Factors
Elevated	Hypothyroidism, steroid use, Rheumatoid arthritis
Reduced	Hyperthyroidism

Table 3. Advantages and limitations of cystatin C in GFR estimation

Advantages	Limitations
Possible role as an alternative to serum creatinine or its estimation equations in elderly people prone for muscle mass variation and hence, creatinine generation	Normal range not defined, method of measurements are not standardized for clinical practice
Possible role as an alternative to serum creatinine or its estimation equations in identifying elderly persons with early decline in GFR	The test is neither widely used nor easily available at this time and has higher cost compared to serum creatinine
Serum cystatin C–based GFR estimates were closely comparable to MDRD (abbreviated) estimates and an equation combining it with serum creatinine, age, sex and race yielded the best possible estimates of GFR	Possible increase in its extra-renal excretion in renal insufficiency
	Conflicting studies regarding factors influencing its ability to estimate GFR

MDRD Equation

The original equation was derived from a study of 1628 middle-aged, nondiabetic, chronic renal insufficiency patients that used a directly measured GFR by urinary clearance of ^{125}I-Iothalamate.[8] It has several advantages over the CG equation including providing an estimate of GFR rather than creatinine clearance, and in addition, a greater percent of these estimates are within the clinically useful range for decision making: 90% of the MDRD based estimates were within 30% of the measured GFR compared with about 75% of CG-based estimates. However, the MDRD equation also has several limitations including that it is less accurate at levels above 60 ml/min per 1.73 m^2. Consequently, it may lead to misdiagnosis and misclassification of CKD in individuals with mild renal insufficiency.[1,9] Table 4 shows additional limitations.

There have been some validation studies of the MDRD equation in elderly people concluding that is it is better than the CG equation.[10–12] The most widely used form of MDRD in elderly people is the four variable version or the version that was abbreviated from the original six variable version (shown below). This is especially advantageous for elderly people compared with the CG formula or the creatinine clearance measurement, because it only requires serum creatinine, age, gender, and race, but not weight or any urine collections. Differences in calibration of creatinine assays between laboratories can lead to differences in GFR estimation and thus is an important limitation of estimation equations in general. The four-variable MDRD was therefore re-expressed in 2005 (as shown below) for use with creatinine methods calibrated to the reference assay method. It is important to note that laboratories without calibrations of their serum creatinine assays calibrated to the reference method, the isotope–dilution mass spectrometry (IDMS) method, should report eGFR using the original four-variable MDRD study equation, recognizing it is less accurate, especially at higher levels of GFR.[13]

In recent years, many laboratories in the United States started reporting, along with the serum creatinine, MDRD-based eGFR values in routine chemistry laboratories and, in some instances, with separate values for African Americans and non-African Americans. However, if the value of eGFR is >60 ml/min per 1.73 m^2, no specific values are mentioned but reported simply as >60 ml/min per 1.73 m^2. As mentioned above, this is because of a lack of precision of estimation at higher levels of GFR. If the specific value >60 ml/min per 1.73

Table 4. Limitations of CG and MDRD equations

Equations	Limitations	Examples
Both CG and MDRD equations	Renal or extrarenal conditions affecting steady state of creatinine in plasma	Initially in ARF, when the serum creatinine is fluctuating or a recovering frail cachectic elderly person
	Interference with creatinine's assay	Ketones, glucose, medications such as cephalosporins interfering with assay
	Variations in muscle mass or diet	Extremes of body mass, pure vegetarian diet or protein-rich diet or amputees
	Calibration bias	
CG equation	Values not adjusted for body surface area	Loss of precision in obese individuals
MDRD equation	Reliability and accuracy decreased in extremes of GFR	Healthy adults, dialysis patients
	Lack of validation studies in some ethnic groups	Some Asian ethnic groups
	Dosing of drugs for renal impairment patients was widely published based on creatinine clearance even before the origin of MDRD and is not adapted for it yet	

m^2 is needed for some reason, one can use the web-based MDRD calculators to find it.

A pertinent point here is, in case of elderly people, if such an estimate of GFR is in the range of 60 to 89 ml/min/1.73 m^2 and these individuals have no known kidney damage markers, it is unclear whether all of the reduced GFR is attributable to age-related decline or part of it is caused by existing kidney disease that the current kidney damage markers are unable to identify. According to NHANES III data, about 75% of persons older than 70 yr of age may have a GFR <90 ml/min per 1.73 m^2 and approximately 25% may have a GFR of <60 ml/min per 1.73 m^2. There are no good studies investigating such subsets of elderly persons with decreased GFR but without identifiable evidence of kidney disease with respect to their long-term outcomes. Nevertheless, the NKF-KDOQI recommendation for elderly persons with eGFR in the range of 60 to 89 ml/min per 1.73 m^2 without any kidney damage markers is to assess for CKD risk factors, screen for kidney damage markers, and carry out interventions to decrease risk of kidney injury.

The six variable MDRD equation is as follows:

$$GFR = 170 \times (SCr)^{-0.999} \times (Age)^{-0.176}$$
$$\times 0.762 \text{ (if patient is female)}$$
$$\times 1.18 \text{ (if patient is black)} \times (BUN)^{-0.170} \times (Alb)^{0.318}$$

where BUN is blood urea nitrogen and Alb is albumin.

The abbreviated version or four variable version of the MDRD equation (ml/min per 1.73 m^2) is as follows:

$$GFR = 186 \times (SCr)^{-1.154} \times (Age)^{-0.203}$$
$$\times 0.742 \text{ (if patient is female)} \times 1.212 \text{ (if patient is black)}$$

The re-expressed MDRD equation (abbreviated version; ml/min per 1.73 m^2) after IDMS-traceable calibration is as follows:

$$GFR = 175 \times (SCr)^{-1.154} \times (Age)^{-0.203}$$
$$\times 0.742 \text{ (if patient is female)} \times 1.212 \text{ (if patient is black)}$$

GFR ESTIMATION FROM SERUM CREATININE AND SERUM CYSTATIN C–BASED EQUATIONS

As mentioned above, a recent study involving a pooled analysis of individuals with chronic kidney disease proposed an estimation equation that included serum cystatin C in addition to serum creatinine, age, sex, and race. The study concluded this equation provided the most accurate estimates. However, further studies are needed to confirm this, especially in elderly persons.[2]

$$eGFR = 177.6 \times S_{cr}^{-0.65} \times CysC^{-0.57} \times (Age)^{-0.20}$$
$$\times 0.82 \text{ (if female)} \times 1.11 \text{ (if black)}$$

CONCLUSION

GFR is the best index available to assess kidney function. Except in situations such as drug dosage adjustment and in some cases of offering transplant options, practically, the change in GFR is more important than the absolute cut-off value. Although novel methods such as cystatin C–based ones are explored, GFR estimation is still largely creatinine based. As such, we are faced with a number of limitations, especially in elderly persons, because the variables affecting creatinine tend to be more pronounced because of comorbid conditions. Currently, MDRD is the most widely used method to estimate GFR in elderly persons. However, other methods may be preferred in certain situations, for example, in extremes of weight, using the 24-h collection for creatinine clearance. Caution needs to be exercised to ascertain that the serum creatinine is stable while using any of the estimation methods. Future studies in this field is very important and should focus on issues such as the elderly subset of patients with decreased GFR but no identifiable markers of kidney damage and novel methods of assessing kidney function by attempting to directly assess nephron mass and function instead of expanding the pool of estimation equations.

TAKE HOME POINTS

- All of the currently available methods of estimation of GFR have several limitations in the elderly persons as in the general population
- Serum creatinine and GFR estimation equations can be applied only when creatinine is stable
- Age-related decline in GFR may not always occur as noted in Baltimore Longitudinal Study on Aging and in some elderly persons it may be difficult to differentiate age-related decline from chronic kidney disease
- The MDRD method is currently the most widely used method of estimation in the elderly persons

DISCLOSURES

None.

REFERENCES

*Key References
1. Stevens LA, Coresh J, Greene T, Levey AS: Assessing kidney function—measured and estimated glomerular filtration rate. *N Engl J Med* 354: 2473–2483, 2006*
2. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS: Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 51: 395–406, 2008
3. Shlipak MG: Cystatin C: research priorities targeted to clinical decision making. *Am J Kidney Dis* 51: 358–361, 2008
4. Köttgen A, Selvin E, Stevens LA, Levey AS, Van Lente F, Coresh J: Serum cystatin C in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). *Am J Kidney Dis* 51: 385–394, 2008

5. Munikrishnappa D: Chronic kidney disease (CKD) in the elderly—a geriatrician's perspective. *Aging Male* 10: 113–137, 2007*

6. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976

7. Pedone C, Corsonello A, Incalzi RA: Estimating renal function in older people: a comparison of three formulas. *Age Ageing* 35: 121–126, 2006*

8. 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* 130: 461–470, 1999

9. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P: Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol* 16: 763–773, 2005

10. Fehrman-Ekholm I, Skeppholm L: Renal function in the elderly (>70 years old) measured by means of iohexol clearance, serum creatinine, serum urea and estimated clearance. *Scand J Urol Nephrol* 38: 73–77, 2004

11. Lamb EJ, Webb MC, O'Riordan SE: Using the modification of diet in renal disease (MDRD) and Cockcroft and Gault equations to estimate glomerular filtration rate (GFR) in older people. *Age Ageing* 36: 689–692, 2007*

12. Verhave JC, Fesler P, Ribstein J, du CG, Mimran A: Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. *Am J Kidney Dis* 46: 233–241, 2005

13. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, Van Lente F; Chronic Kidney Disease Epidemiology Collaboration: Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 53: 766–772, 2007

REVIEW QUESTIONS: LIMITATIONS OF VARIOUS FORMULAE AND OTHER WAYS OF ASSESSING GFR IN THE ELDERLY: IS THERE A ROLE FOR CYSTATIN C?

1. An active, 87-yr-old African-American female resident from a nursing home develops pneumonia requiring prolonged hospitalization and complicated by diarrhea. She returns to the nursing home on a common oral antibiotic for one more week duration in addition to metronidazole. She is noticeably weak, frail, and has lost significant weight. A chemistry panel obtained on her return to the nursing home shows a creatinine of 1 mg/dl, which is an increase of 0.1 mg/dl from the previous one obtained at the nursing home before her hospitalization. The facility pharmacy consultant reviews the antibiotic dose and recommends a significant decrease in dosage. Presuming the consultant made the right recommendation, what is the most likely explanation warranting a decrease in the dose?
   a. Mild decline in kidney function
   b. Mild increased creatinine
   c. Significant loss of muscle mass and kidney function
   d. Pharmacist is likely incorrect

2. A robust, healthy elderly person 72 yr of age with no medical condition comes to your nephrology clinic. He inquires if the family needs to start planning for him to be initiated on dialysis anytime soon. On reviewing the records, you conclude that his eGFR is approximately 82 ml/min per 1.73 m^2 based on MDRD without any known risk factors for kidney disease. Which of the following statements is true?
   a. eGFR by MDRD is less accurate at GFR above 60 ml/min per m^2
   b. Periodic follow-up for risk factor assessment recommended
   c. MDRD is currently the most widely used equation for eGFR in elderly persons
   d. All of the above
   e. None of the above

3. The following statements are true of cystatin C in the elderly except:
   a. serum cystatin C likely correlates better with GFR than does serum creatinine alone in a frail elderly with mild kidney dysfunction
   b. Increased tubular secretion compared with creatinine
   c. Steroids may influence its level
   d. Age and muscle mass may also influence its level according to some studies