Medication dosing in adult patients with reduced lean body mass and kidney injury: A focus on cystatin C

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Purpose: Creatinine-based estimates of glomerular filtration rate (GFR) have been the standard for classifying kidney function and guiding drug dosing for over 5 decades. There have been many efforts to compare and improve different methods to estimate GFR. The National Kidney Foundation recently updated the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations without race for creatinine (CKD-EPIcr_R) and creatinine and cystatin C (CKD-EPIcr-cys_R), and the 2012 CKD-EPI equation based on cystatin C (CKD-EPIcys) remains. The focus of this review is to highlight the importance of muscle atrophy as a cause for overestimation of GFR when using creatinine-based methods.

Summary: Patients with liver disease, protein malnutrition, inactivity, denervation, or extensive weight loss may exhibit markedly lower creatinine excretion and serum creatinine concentration, leading to overestimation of GFR or creatinine clearance when using the Cockcroft-Gault equation or CKD-EPIcr (deindexed). In some cases, estimated GFR appears to exceed the physiological normal range (eg, >150 mL/min/1.73 m^2). Use of cystatin C is recommended when low muscle mass is suspected. One would expect discordance between the estimates such that CKD-EPIcys < CKD-EPIcr-cys < CKD-EPIcr ≈ Cockcroft-Gault creatinine clearance. Clinical evaluation can then occur to determine which estimate is likely accurate and should be used for drug dosing.

Conclusion: In the setting of significant muscle atrophy and stable serum creatinine levels, use of cystatin C is recommended, and the resulting estimate can be used to calibrate interpretation of future serum creatinine measurements.

Keywords: clearance, creatinine, creatinine clearance, cystatin C, glomerular filtration rate, renal function

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Serum concentrations of creatinine are remarkably consistent when measured over time in stable patients. This stability has been noted even in the intensive care unit (ICU) setting in patients without renal injury or hemodynamic instability.[1] If glomerular filtration rate (GFR) exhibited significant inter-occasion variability, greater variability in serum creatinine levels would be expected. Creatinine clearance (CL_{CR}) is measured based on the ratio of creatinine excretion to serum concentration, and CL_{CR} is associated with moderate inter-occasion variability.[2] Most of this variability is due to variability in excretion.[3,4] When compared to measured CL_{CR}, both estimated CL_{CR} and estimated GFR (eGFR) from the Chronic Kidney Disease Epidemiology Collaboration equation with cystatin C (CKD-EPIcys) appear to lack accuracy[5]; however, if the measured CL_{CR} exhibits moderate inter-occasion variability, the test methods will also reflect this variability. Methods to estimate GFR are accurate when they successfully predict the average GFR for the individual as a constant, and factors including sex, age, and body size metrics contribute to this prediction. It is possible that formulas such as the Cockcroft-Gault (CG)

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equation and the CKD-EPI equations are able to filter out the day-to-day measurement error, which would be a good thing.

Extremes of muscle mass, both high and low, are not considered by eGFR equations. Bodybuilders and people who take creatine are known to have increased creatinine excretion, while patients with accelerated sarcopenia and/or muscle atrophy have low excretion.[6] The equations are designed based on excretion for the average person adjusted for covariates. The CKD-EPI equation for creatinine (CKD-EPIcr) bypasses creatinine excretion and attempts to predict GFR directly; however, the observed serum concentration still reflects individuals' creatinine excretion relative to CL_{CR}. Sarcopenia refers to the gradual loss of muscle that occurs with advancing age. Muscle atrophy on the other hand results from denervation, disuse, cancer, malnutrition, and other conditions.[7] With muscle atrophy, there can be rapid loss of muscle mass, and this would result in a marked reduction in creatinine excretion and serum concentration. In a retrospective study that included approximately 5,000 patients, a U-shaped relationship was observed between mortality and eGFR.[8] When the values for eGFR were corrected for patients with low creatinine excretion (a surrogate for sarcopenia), the increase in mortality seen with the higher values of eGFR was eliminated.[9]

Estimated CL_{CR} and eGFR have been stated to perform poorly as a measure of renal function.[10] However, critical evaluation of available data suggests that these methods have performed well for more than 50 years for their intended purpose. The CG method has been used extensively to categorize renal function and inform drug dosing for drugs that are renally eliminated. Weight loss is not an unexpected problem in hospitalized patients given the prevalence of malnutrition risk of 32.7% in one study including data from 9,959 adult patients.[11] Weight loss in hospitalized patients is a concern regardless of initial body mass index (BMI), as being overweight or obese does not protect against weight loss–associated mortality,[12] and it presents challenges for adjusting the dosing of renally eliminated medications based on eGFR. Within a recent 6-month period at our academic medical center, we identified several cases of patients with a recent history of substantial weight loss who had creatinine-based eGFR values far exceeding usual measured values, which rarely surpass 150 mL/min/1.73 m^2 in adults, regardless of kidney pathology.[13] Although the first certified reference material for cystatin C in human serum was developed in 2010,[14] it was over a decade before our health system obtained testing capabilities for serum cystatin C concentrations and implemented reporting from the CKD-EPI equation for cystatin C (CKD-EPIcys). These changes led us to consider the use of cystatin C testing to help formulate medication dosing regimens in adult patients with reduced lean body mass and kidney injury, particularly in light of recent recommendations by a task force of the National Kidney Foundation and American Society of Nephrology suggesting the use of cystatin C in combination with or as an alternative to serum creatinine as a filtration marker.[15] The purpose of this paper is to describe the potential usefulness of cystatin C monitoring in developing dosing regimens for renally eliminated medications in patients with substantial reductions in lean tissue that reduce the performance of creatinine as a marker of GFR.

KEY POINTS

- Weight loss presents challenges for adjusting the dosing of renally eliminated medications based on estimations of glomerular filtration rate (GFR).
- There is no standardized, evidence-based approach to evaluate estimated GFR values for medication dosing in adult patients with reduced lean body mass and kidney injury.
- Clinicians should consider the use of cystatin C testing to help formulate medication dosing regimens in adult patients with reduced lean body mass and kidney injury.

Cystatin C for estimation of GFR

Cystatin C is a polypeptide that is synthesized by all nucleated cells and produced at a regular rate by mammals. Its molecular mass is approximately 13.3 kDa, which allows this substance to pass through the glomerular membrane, where it is reabsorbed in the proximal renal tubule and catabolized. Serum concentrations of cystatin C inversely correlate with GFR and can be used to estimate GFR. Readers are referred to an excellent review on cystatin C.[16] The CKD-EPIcys equation was developed to estimate GFR in 2012. This study involved over 5,300 individuals with GFR determined by iothalamate clearance, and regression equations were developed to estimate GFR using serum cystatin C concentration (Table 1). The equations were externally evaluated in a separate population of 1,119 individuals.[19] Additional equations have been updated to estimate GFR using serum creatinine (CKD-EPIcr_R) or both creatinine and cystatin C (CKD-EPIcr-cys_R). In the full population, the equation using both biomarkers is more accurate than equations relying on one biomarker.[15] When there is large discordance between CKD-EPIcr_R and CKD-EPIcys, the discordance is usually explained by an underlying condition of the patient. When the CKD-EPIcr-cys_R equation is used in such a patient, the resulting estimate will be between the 2 GFR estimates from the equations using single biomarkers, and one of the predictions is probably invalid. Despite the availability of serum cystatin C testing, the turnaround time is about 4 days. Thus, ordering of cystatin C testing has been selective and infrequent. Results from the CKD-EPIcys_R equation can

Table 1. Equations for Calculations

Equation	Definition
CKD-EPIcr_R	eGFR (mL/min/1.73 m^2) = 142 × min(Scr/*k*,1)$^{\alpha}$ × max(Scr/*k*,1)$^{-1.200}$ × 0.9938^{age} × 1.012 (if female), where Scr is serum creatinine, *k* is 0.7 for females and 0.9 for males, $^{\alpha}$ is –0.241 for females and –0.302 for males, min indicates the minimum of Scr/*k* or 1, and max indicates the maximum of Scr/*k* or 1.[15,17]
CKD-EPIcr-cys_R	eGFR (mL/min/1.73 m^2) = 135 × min(Scr/*k*,1)$^{\alpha}$ × max(Scr/*k*,1)$^{-0.544}$ × min(Scys/0.8,1)$^{-0.323}$ × max(Scys/0.8,1)$^{-0.778}$ × 0.9961^{age} × 0.963 (if female), where Scr is serum creatinine, Scys is serum cystatin C, *k* is 0.7 for females and 0.9 for males, α is –0.219 for females and –0.144 for males, min indicates the minimum of Scr/*k* or 1, and max indicates the maximum of Scr/*k* or 1.[15,17]
CKD-EPIcys (2012)	eGFR (mL/min/1.73 m^2) = 133 × min(Scys/0.8,1)$^{-0.499}$ × max(Scys/0.8,1)$^{-1.328}$ × 0.996^{age} × 0.932 (if female), where Scys is serum cystatin C, min indicates the minimum of Scys/0.8 or 1, and max indicates the maximum of Scys/0.8 or 1.[15,17]
Cockcroft-Gault	CL_{CR} (mL/min) = (140 – age) × (weight, kg) × (0.85 if female)/(72 × Scr), where CL_{CR} is creatinine clearance.
Estimated urinary creatinine excretion	Estimated urinary creatinine excretion (mg/24 hours) = –9.04 × age (years) + 8.03 × weight (kg) + 0.66 × height (cm) + 188.59 (if male) – 32.11 × Scr (mg/dL) + 779.14, where Scr is serum creatinine.[18]
Measured urinary creatinine excretion	Measured urinary creatinine excretion (mg/24 hours) = Scr (mg/dL) × CL_{CR} (mL/min) × 14.4, where 14.4 is a correction for units (1,440 min/day and going from mg/dL to mg/mL), Scr is serum creatinine, and CL_{CR} is creatinine clearance.

Abbreviations: CKD-EPIcr-cys_R, Chronic Kidney Disease Epidemiology Collaboration creatinine and cystatin C equation refit without the race variable; CKD-EPIcr_R. Chronic Kidney Disease Epidemiology Collaboration creatinine equation refit without the race variable; CKD-EPIcys (2012), Chronic Kidney Disease Epidemiology Collaboration cystatin C equation from 2012; eGFR, estimated glomerular filtration rate.

be used to calibrate the eGFR result and allow continued monitoring with creatinine-based eGFR.

It is important to stress that we are discussing the *potential* usefulness of cystatin C monitoring in patients with reductions in muscle mass and muscle atrophy. The approach suggested in this paper is hypothesis generating, as none of the patient populations serving as the basis for eGFR equation comparisons had markedly reduced muscle mass or malnutrition,[19] conditions in which cystatin C might exhibit better performance than creatinine given its constant rate of production by nucleated cells and lack of alteration in association with changes in lean tissue mass that can markedly affect creatinine production.[20] A sarcopenia index (SI) has been developed, which is the serum creatinine concentration (mg/dL) divided by the serum cystatin C concentration (mg/L) × 100.[21] Other publications have used the ratio without multiplying by 100. An SI of less than 80 for females and less than 100 for males indicates sarcopenia; however, much lower values were seen in the patients who inspired this article. Recently, a high-profile article suggested using different CKD-EPI equations based on patient-specific factors. In the example presented, the results for GFR ranged from 32 to 64 mL/min/1.73 m^2 and the lowest value was selected given the patient's low muscle mass.[22]

Clinical considerations in specific patient populations

Critically ill patients present a unique challenge with respect to GFR assessment, as lean tissue loss is common with increasing lengths of stay and there are no good estimating alternatives to computed tomography to assess lean body mass.[23] Some data have suggested that normal intraday variation in cystatin C–associated eGFR values is relatively small, with 95% of test results varying by less than 10% between sampling times for patients in the ICU setting.[1] Additionally, other studies have suggested that common laboratory abnormalities such as hyperglycemia have little effect on cystatin C levels[24] and that ICU procedures such as dialysis remove relatively little cystatin C.[25] However, both measured CL_{CR} and all eGFR equations perform poorly in critically ill patients with early-stage acute kidney injury when compared to gold-standard measurements of kidney function.[26] Given the increased mortality seen when using estimates from CKD-EPIcr (>75 mL/min/1.73 m^2) and the elimination of this finding when the values were corrected for creatinine excretion in patients with sarcopenia, serum cystatin C–based eGFR is superior to creatinine-based GFR with respect to long-term prognosis at ICU discharge.[27]

In patients with primary neuromuscular diseases who have reduced muscle mass, all eGFR equations overestimate measured GFR, although cystatin C–based equations have less bias and are more accurate than creatinine-based equations. This was demonstrated in a recently published

study involving 145 patients with primary neuromuscular disease who had kidney function measured by iohexol clearance with blood sampling for estimation of GFR by creatinine and cystatin C.[28] All 4 equations based on creatinine, cystatin C, or a combination of these 2 parameters overestimated kidney function by 22 to 32 mL/min/1.73 m^2, but eGFR determined using cystatin C had the lowest overall bias (22 mL/min/1.73 m^2; 95% confidence interval, 19-25 mL/min/1.73 m^2) and the best accuracy in patients with reduced kidney function (5.9% at 30-59 mL/min/1.73 m^2), as defined by the proportion of eGFR values within 10% of the measured clearance.

Serum cystatin C levels are elevated in hyperthyroidism and lowered in hypothyroidism.[29] Cystatin C is not affected by liver function and is better at predicting measured GFR than creatinine,[30] but the poor performance of both creatinine- and cystatin C–based eGFR equations limits their usefulness in patients following orthotopic liver transplantation.[31] Similarly, both creatinine- and cystatin C–based eGFR equations exhibit poor performance in patients with decompensated heart failure.[32] Cystatin C elevations are found in patients with a variety of inflammatory conditions and proteinuria, including obesity, although the clinical importance of such elevations needs further study.[33] Corticosteroids have been cited as inducing cystatin C; however, this effect does not appear to be dose dependent and does not affect the performance of cystatin C in identifying acute kidney injury.[34]

Serum cystatin C and CKD-EPIcys for drug dosing

A systematic review of use of cystatin C for drug dosing was conducted at the Mayo Clinic up to 2017. The authors identified 28 articles involving 16 different drugs that examined the performance of cystatin C–based eGFR in predicting drug concentrations or drug clearance. Cystatin C–based eGFR was at least as accurate as CL_{CR} for renal dosing of drugs. Vancomycin was the most studied drug; however, the endpoint was trough concentration rather than clearance.[35] Consequently, the dosing interval relative to half-life would be a confounding variable. Food and Drug Administration guidance pertaining to conduct of pharmacokinetic studies in individuals with impaired renal function suggests examining the relationship between CLs and CL_{CR}, where CLs = slope × CL_{CR}/eGFR + intercept.[36] The renal clearance is the slope times the eGFR, while the intercept is the nonrenal clearance. Typically, individuals are grouped by eGFR category: ≥60 mL/min, 30-59 mL/min, 15-29 mL/min, and <15 mL/min (not on dialysis). Data will exist on the target dosing for individuals with normal renal function based on preclinical studies, safety studies, and perhaps a phase 2 study. The goal is usually to develop a dose for each renally impaired group that will provide similar exposure (area under the concentration-time curve, or AUC) as for individuals without renal impairment. For example, those with an eGFR of 30-59 mL/min might require half the dose of individuals without renal impairment to achieve a similar AUC. The problem with this approach is that one eGFR method may provide a result of 58 mL/min while another method gives a result of 62 mL/min. These values are not significantly different but result in a categorical difference in the dose recommendation. If eGFR were used to estimate drug clearance, the dose regimen required to produce a target AUC could be calculated. Subsequently, the dose could be rounded to a convenient value while eliminating the problem introduced by arbitrary breakpoints.

Several studies have been conducted in elderly patients, who represent one group that may present with accelerated sarcopenia. The pharmacokinetics of ceftriaxone were studied in 24 elderly patients. Frailty was noted in 21 of the 24 patients using the Edmondton frailty scale including grip strength. The mean (interquartile range) BMI was 27.5 (22-33) kg/m^2, CL_{CR} was 48 (26-63) mL/min, CKD-EPIcr-cys eGFR was 38 (35-41.5) mL/min, and CKD-EPIcys eGFR was 36 (23-49) mL/min. Population pharmacokinetic modeling revealed that CKD-EPIcr-cys eGFR was the most predictive covariate, followed by CKD-EPIcys eGFR.[37] Ampicillin/sulbactam was studied in 105 elderly patients with pneumonia. Mean (SD) renal function measurements included CL_{CR} of 45.1 (36.8) mL/min, CKD-EPIcr eGFR of 57.2 (53.8) mL/min, and CKD-EPIcys eGFR of 38.6 (17.8) mL/min. The correlation between ampicillin clearance and the renal function measurements was 0.4913, 0.3333, and 0.7374, respectively, indicating that CKD-EPIcys eGFR is the best predictor of ampicillin clearance.[38] In a group of 25 nonobese elderly patients with hypoalbuminemia and chronic kidney disease, CKD-EPIcr-cys performed slightly better than CKD-EPIcys and both of these were better than CL_{CR}. The median (range) values for CL_{CR}, CKD-EPIcr eGFR, and CKD-EPIcys eGFR were 31.9 (14.3-100), 47.6 (18.8-93.7), and 34.6 (9.4-79.4) mL/min, respectively.[39] Vancomycin clearance was studied in patients with persistent inflammation, immunosuppression, and catabolism syndrome, defined by an ICU stay of at least 14 days, inflammation (C-reactive protein concentration of >3 mg/dL), immunosuppression (lymphocyte count of <800/μL), and catabolism (albumin concentration of <0.003 g/dL and weight loss of more than 10% during the ICU stay). The relative differences in renal function measures were typical for patients with severe muscle loss/atrophy, with mean (SD) CL_{CR} = 106 (70) mL/min/1.73 m^2, CKD-EPIcr eGFR = 89 (40) mL/min/1.73 m^2, CKD-EPIcr-cys eGFR = 65 (33) mL/min/1.73 m^2, and CKD-EPIcys eGFR = 49 (29) mL/min/1.73 m^2. The authors reported that CKD-EPIcr-cys was the best covariate to predict vancomycin clearance; however, this was coupled with a population pharmacokinetic model and the CKD-EPIcr-cys values were not deindexed.[40]

Differences in eGFR calculations related to lean tissue loss have implications for medication dosing in addition to more referenced investigations of kidney injury assessment. Take the case of a 36-year-old male who is 187 cm tall, weighs 55 kg (down from 93 kg approximately 4 months earlier), and has steady-state serum creatinine and cystatin C levels of 1.26 mg/dL and 3.18 mg/dL, respectively. In this example, the patient is not in one of the special populations for which the interpretation of cystatin C levels might be hindered. Using the CG equation, the patient's estimated CL_{CR} is 63 mL/min at baseline. Using the CKD-EPIcr_R equation, the patient's eGFR is 76 mL/min/1.73 m^2 or 77 mL/min (deindexed for body surface area). Using the CKD-EPIcr-cys_R equation, the patient's eGFR is 33 mL/min/1.73 m^2 or 34 mL/min deindexed, and finally, using the CKD-EPIcys equation, the patient's eGFR is 18 mL/min/1.73 m^2 or 19 mL/min deindexed. Now consider that the patient will receive a medication that requires dosage adjustment for kidney dysfunction and the CG equation for CL_{CR} is mentioned in the approved labeling. The clinician must decide which of the eGFR estimates is most likely reflective of the patient's actual renal function. In this situation with differing eGFR estimates depending on creatinine or cystatin C variables in the calculations, it is useful to determine the patient's estimated urinary excretion of creatinine assuming normal lean tissue mass, which typically would approximate 1,167 mg/day.[41] On the other hand, if we assume that each of the values calculated for eGFR is correct, the estimated urinary excretion rate of creatinine would be approximately 1,397 mg/day using the CKD-EPIcr_R estimate, 617 mg/day using the CKD-EPIcr-cys_R estimate, and 379 mg/day using the CKD-EPIcys estimate, with an estimated 10% increase to correct for the tubular secretion of creatinine.[18] The last value of 379 mg/day is roughly one-third of the patient's estimated creatinine excretion rate of 1,167 mg/day, a figure that seems most reflective of the patient's actual creatinine excretion given the weight loss of 40% over the past 4 months. A way to corroborate or refute this estimate of creatinine excretion would be 24-hour urine collection to measure creatinine excretion, assuming the patient is not critically ill. If the patient is assumed to not be critically ill and the actual excretion approximately equals the predicted excretion, this would be consistent with low muscle mass. The longstanding use of the CG equation for medication dosing is predicated on the patient having normal muscle mass and thus normal creatinine excretion. If we find that the actual 24-hour creatinine excretion (measured or predicted based on cystatin C) is lower, the CL_{CR} estimate needs to be adjusted by that factor (0.32 in the example above). The 2021 National Kidney Foundation and American Society of Nephrology taskforce to estimate GFR in adults endorsed the use of cystatin C and recommended "national efforts to facilitate increased, routine, and timely use of cystatin C, especially to confirm eGFR in adults."[15]

Conclusion

Assuming cystatin C monitoring is available, its use should be considered to potentially improve GFR estimation in hospitalized patients receiving renally eliminated medications who have had substantial weight loss (>5%), have suspected muscle atrophy, or have estimations of CL_{CR} (CG equation) or eGFR values exceeding anticipated values or the normal physiological range (eg, an eGFR of >150 mL/min/1.73 m^2). There is no standardized, evidence-based approach to eGFR evaluation for medication dosing in adult patients with reduced lean body mass and kidney injury. Until additional research is forthcoming, this paper describes some of the more important considerations when estimating kidney function in these patients by considering factors affecting both the production and excretion of the creatinine- and cystatin C–based biomarkers. Future studies are urgently needed that evaluate different approaches in such patients, preferably prospective investigations with an evaluation of clinically important outcomes.

Disclosures

The authors have declared no potential conflicts of interest.

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