CASE IN POINT

My Kidney Is Fine, Can't You Cystatin C?

Capt Alexander Beckstead, MD, USAF[a]; H. Reed Holmes, MD[b]; Capt Vi Tran, MD, USAF[a]; Bhagwan Dass, MD[c]

Background: Independent of age, sex, and body composition, individuals of African American race and individuals with high muscle mass have elevated serum creatinine (sCr) levels on average that may result in overestimation of chronic kidney disease (CKD). We present a misdiagnosed case of CKD based on sCr levels, illustrating the utility of cystatin C (CysC) confirmation testing to answer the question: Can confirmation screening of kidney function with CysC in African American patients and patients with high muscle mass reduce the misdiagnosis of CKD?

Case Presentation: A 35-year-old African American man with a history of well-controlled HIV was found to have consistently elevated creatinine (Cr). We diagnosed CKD stage 3A based on the estimated glomerular filtration rate (eGFR). Further evaluation showed isolated elevation of sCr with unremarkable urinalysis and other laboratory tests. sCr elevation predated diagnosis and HIV treatment. A CysC-based eGFR ($eGFR_{cys}$) test confirmed the absence of CKD.

Conclusions: The 2009 CKD Epidemiology Collaboration calculation of eGFR based on sCr concentration uses age, sex, and race, with an updated recommendation in 2021 to exclude race. Both equations are less accurate in African American patients, individuals taking medications that interfere with sCr secretion and assay, and patients taking creatine supplements or high protein intake. These clinical scenarios decrease sCr-based eGFR ($eGFR_{Cr}$) but do not change measured eGFR or $eGFR_{Cys}$. Using sCr and serum cystatin C ($eGFR_{Cr\text{-}Cys}$) yields better concordance to measured eGFR across all races than does eGFR estimation based on Cr alone. Confirmation with CysC can avoid misdiagnosis, incorrect dosing of drugs, and inaccurate representation of the fitness for duty.

Author affiliations can be found at the end of this article.
Correspondence: Bhagwan Dass (bhagwan.dass@va.gov)

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Clinicians usually measure renal function by using surrogate markers because directly measuring glomerular filtration rate (GFR) is not routinely feasible in a clinical setting.[1,2] Creatinine (Cr) and cystatin C (CysC) are the 2 main surrogate molecules used to estimate GFR.[3]

Creatine is a molecule nonenzymatically converted into Cr, weighing only 113 Da in skeletal muscles.[4] It is then filtered at the glomeruli and secreted at the proximal tubules of the kidneys. However, serum Cr (sCr) levels are affected by several factors, including age, biological sex, liver function, diet, and muscle mass.[5] Historically, sCr levels also are affected by race.[5] In an early study of factors affecting accurate GFR, researchers reported that self-identified African American patients had a 16% higher GFR than those who did not when using Cr.[6] Despite this, the inclusion of Cr on a basic metabolic panel has allowed automatic reporting of an estimated GFR using sCr ($eGFR_{Cr}$) to be readily available.[7]

In comparison to Cr, CysC is an endogenous protein weighing 13 kDa produced by all nucleated cells.[8,9] CysC is filtered by the kidney at the glomeruli and completely reabsorbed and catabolized by epithelial cells at the proximal tubule.[9] Since production is not dependent on skeletal muscle, there are fewer physiological impacts on serum concentration of CysC. Levels of CysC may be elevated by factors shown in the Table.

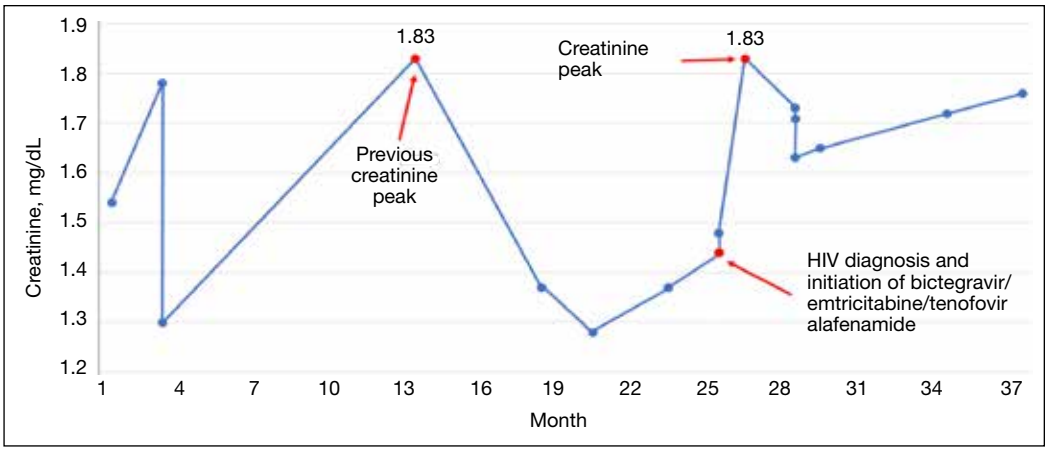
ESTIMATING GLOMERULAR FILTRATION RATES

Multiple equations were developed to mitigate the impact of extraneous factors on the accuracy of an $eGFR_{Cr}$. The first widely used equation that included a variable adjustment for race was the Modification of Diet in Renal Disease study, presented in 2006.[10] The equation increased the accuracy of $eGFR_{Cr}$ further by adjusting for sex and age. It was followed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation in 2009, which was more accurate at higher GFR levels.[11]

CysC was simultaneously studied as an alternative to Cr with multiple equation iterations shown to be viable in various populations as early as 2003.[12-15] However, it was not until 2012 that an equation for the use of CysC was offered for widespread use as an alternative to Cr alongside further refinement of the CKD-EPI equation for Cr.[16] A new formula was presented in 2021 to use both sCr and serum CysC levels to obtain a more accurate estimation of GFR.[17] Research continues its effort to accurately estimate GFR for diagnosing kidney disease and assessing comorbidities relating to decreased kidney function.[3]

All historical equations attempted to mitigate the potential impact of race on sCr level when calculating $eGFR_{Cr}$ by assigning a separate variable for African American patients.

FIGURE Patient's Creatinine Levels and Timeline of Elevation[a]



[a]After bictegravir/emtricitabine/tenofovir alafenamide initiation at month 25 and a similar peak to prior of 1.83 mg/dL at month 26 without renal injury.

As an unintended adverse effect, these equations may have led to discrimination by having a different equation for African American patients.[18] Moreover, these Cr-based equations remain less accurate in patients with varied muscle mass, such as older patients, bodybuilders, athletes, and individuals with varied extremes of daily protein intake.[1,8,9,19] Several medications can also directly affect Cr clearance, reducing its ability to act as a surrogate for kidney function.[1] In this case report, we discuss an African American patient with high muscle mass and protein intake who was initially diagnosed with kidney disease based on an elevated Cr and found to be misdiagnosed based on the use of CysC for a more accurate GFR estimation.

CASE PRESENTATION

A 35-year-old African American man serving in the military and recently diagnosed with HIV was referred to a nephrology clinic for further evaluation of an acute elevation in sCr. Before treatment for HIV, a brief record review showed a baseline Cr of about 1.3 mg/dL, with an $eGFR_{Cr}$ of 75 mL/min/1.73 m^2.[20] In the same month, the patient was prescribed bictegravir/emtricitabine/tenofovir alafenamide, an HIV drug with nephrotoxic potential.[21] The patient's total viral load remained low, and CD4 count remained > 500 after initiation of the HIV treatment. He was in his normal state of health and had no known contributory history before his HIV diagnosis. Cr readings peaked at 1.83 mg/dL after starting the HIV treatment and remained elevated to 1.73 mg/dL over the next few months, corresponding to CKD stage 3A. Because bictegravir/emtricitabine/tenofovir alafenamide is cleared by the kidneys and has a nephrotoxic profile, the clinical care team considered dosage adjustment or a medication switch given his observed elevated $eGFR_{Cr}$ based on the CKD-EPI 2021 equation for Cr alone. It was also noted that the patient had a similar Cr spike to 1.83 mg/dL in 2018 without any identifiable renal insult or symptoms (Figure).

Diagnostic Evaluation

The primary care team ordered a renal ultrasound and referred the patient to the nephrology clinic. The nephrologist ordered the following laboratory studies: urine microalbumin to Cr ratio, basic metabolic panel (BMP), comprehensive metabolic panel (CMP), urinalysis, urine protein, urine Cr, parathyroid hormone level, hemoglobin A_{1c}, complement component 3/4 panels, antinuclear and antineutrophil cytoplasmic antibodies titers, glomerular basement membrane antibody titer, urine light chains, serum protein electrophoresis, κ/λ ratio, viral hepatitis panel, and rapid plasma reagin testing. Much of this laboratory evaluation served to rule out any secondary causes of kidney disease, including autoimmune disease, monoclonal or polyclonal gammopathies, diabetic nephropathy or glomerulosclerosis, and nephrotic or nephritic syndromes.

TABLE Factors to Consider When Using Creatinine and Cystatin C[a]

Biomarker	Creatinine	Cystatin C
Source	Breakdown product of creatine phosphate in skeletal muscle	13 kDa protease inhibitor secreted steadily by all nucleated cells
Biomarker level factors	Race and ethnicity other than US and European Black and White patients; sex; age; extremes of muscle mass; high protein diet; ingesting cooked meat; creatine supplements; muscle wasting diseases (Duchenne muscular dystrophy, etc); and liver function	Race and ethnicity other than US and European Black and White patients; disorders of thyroid function; administration of corticosteroids; inflammation and high cell turnover states; common genetic variants; and obesity
Tubular secretion/ absorption	Freely filtered at renal glomeruli; actively secreted by proximal tubule; no reabsorption; and tubular secretion increased in chronic kidney disease (decreased serum creatinine levels)	No tubular secretion; complete reabsorption and catabolism in proximal tubules; and increased serum levels in chronic kidney disease

[a]Differences include sources within the body, effects by factors, and methods of filtration by the kidneys. Note that cystatin C levels are independent of muscle mass, high protein diet, and creatine supplementation, which is different from its effects on creatinine levels.

All laboratory studies returned within normal limits; no proteinuria was discovered on urinalysis, and no abnormalities were visualized on renal ultrasound. Bictegravir/emtricitabine/tenofovir alafenamide nephrotoxicity was highest among the differential diagnoses due to the timing of Cr elevation coinciding with the initiation of the medications. The patient's CysC level was 0.85 mg/dL with a calculated $eGFR_{Cys}$ of 125 mL/min/1.73 m^2. The calculated sCR and serum cystatin C ($eGFR_{Cr\text{-}Cys}$) using the new 2021 equation and when adjusting for body surface area placed his eGFR at 92 mL/min/1.73 m^2.[20]

The patient's $eGFR_{Cys}$ reassured the care team that the patient's renal function was not acutely or chronically impacted by bictegravir/emtricitabine/tenofovir alafenamide, resulting in avoidance of unnecessary dosage adjustment or discontinuation of the HIV treatment. The patient reported a chronic habit of protein and creatine supplementation and bodybuilding, which likely further compounded the discrepancy between $eGFR_{Cr}$ and $eGFR_{Cys}$ and explained his previous elevation in Cr in 2018.

Follow-up

The patient underwent serial monitoring that revealed a stable Cr and unremarkable eGFR, ruling out CKD. There has been no evidence of worsening kidney disease to date, and the patient remained on his initial HIV regimen.

DISCUSSION

This case shows the importance of using CysC as an alternative or confirmatory marker compared with sCr to estimate GFR in patients with high muscle mass and/or high creatine intake, such as many in the US Department of Defense (DoD) and US Department of Veterans Affairs (VA) patient populations. In the presented case, recorded Cr levels climbed from baseline Cr with the initiation of bictegravir/emtricitabine/tenofovir alafenamide. This raised the concern that HIV treatment was leading to the development of kidney damage.[22]

Diagnosis of kidney disease as opposed to the normal decline of eGFR with age in individuals without intrinsic CKD requires GFR ≥ 60 mL/min/1.73 m^2 with kidney damage (proteinuria or radiological abnormalities, etc) or GFR < 135 to 140 mL/min/1.73 m^2 minus the patient's age in years.[23] The patient's Cr peak at 1.83 mg/dL in 2018 led to an inappropriate diagnosis of kidney disease stage 3a based on an $eGFR_{Cr}$ (2021 equation) of 52 mL/min/1.73 m^2 when not corrected for body surface area.[20] However, using the new 2021 equation using both Cr and CysC, the patient's $eGFR_{Cr\text{-}Cys}$ was 92 mL/min/1.73 m^2 after a correction for body surface area.

The 2009 CKD-EPI recommended the calculation of eGFR based on SCr concentration using age, sex, and race while the 2021 CKD-EPI recommended the exclusion of race.[3] Both equations are less accurate in African American patients, individuals taking medications that interfere with Cr secretion and assay, and patients taking creatine supplements, high daily protein intake, or with high muscle mass.[7] These settings result in a decreased $eGFR_{Cr}$ without corresponding $eGFR_{Cys}$ changes. Using SCr and CysC together, the $eGFR_{Cr\text{-}Cys}$ yields improved concordance to measured GFR across race groups compared to GFR estimation based

on Cr alone, which can avoid unnecessary expensive diagnostic workup, inappropriate kidney disease diagnosis, incorrect dosing of drugs, and accurately represent the military readiness of patients. Interestingly, in African American patients with recently diagnosed HIV, CKD-EPI using both Cr and CysC without race inclusion led to only a 2.9% overestimation of GFR and was the only equation with no statistically significant bias compared with measured GFR.[24]

A March 2023 case involving an otherwise healthy 26-year-old male active-duty US Navy member with a history of excessive protein supplement intake and intense exercise < 24 hours before laboratory work was diagnosed with CKD after a measured Cr of 16 mg/dL and an $eGFR_{Cr}$ of 4 mL/min/1.73 m^2 without any other evidence of kidney disease. His CysC remained within normal limits, resulting in a normal $eGFR_{Cys}$ of 121 mL/min/1.73 m^2, indicating no CKD. His Cr and eGFR recovered 10 days after his clinic visit and cessation of his supplement intake. These findings may not be uncommon given that 65% of active-duty military use protein supplements and 38% use other performance-enhancing supplements, such as creatine, according to a study.[25]

Unfortunately, the BMP/CMP traditionally used at VA centers use the $eGFR_{Cr}$ equation, and it is unknown how many primary care practitioners recognize the limitations of these metabolic panels on accurate estimation of kidney function. However, in 2022 an expert panel including VA physicians recommended the immediate use of $eGFR_{Cr\text{-}Cys}$ or $eGFR_{Cys}$ for confirmatory testing and potentially screening of CKD.[26] A small number of VAs have since adopted this recommendation, which should lead to fewer misdiagnoses among US military members as clinicians should now have access to more accurate measurements of GFR.

The VA spends about $18 billion (excluding dialysis) for care for 1.1 to 2.5 million VA patients with CKD.[27] The majority of these diagnoses were undoubtedly made using the $eGFR_{Cr}$ equation, raising the question of how many may be misdiagnosed. Assessment with CysC is currently relatively expensive, but it will likely become more affordable as the use of CysC as a confirmatory test increases.[5] The cost of a sCr test is about $2.50, while CysC costs about $10.60, with variation from laboratory to laboratory.[28] By comparison, a renal ultrasound costs $99 to $140 for uninsured patients.[29] Furthermore, the cost of CysC testing is likely to trend downward as more facilities adopt the use of CysC measurements, which can be run on the same analytical equipment currently used for Cr measurements. Currently, most laboratories do not have established assays to use in-house and thus require CysC to be sent out to a laboratory, which increases result time and makes Cr a more attractive option. As more laboratories adopt assays for CysC, the cost of reagents will further decrease.

Given such considerations, confirmation testing of kidney function with CysC in specific patient populations with decreased $eGFR_{Cr}$ without other features of CKD can offer great medical and financial benefits. A 2023 KDIGO report noted that many individuals may be mistakenly diagnosed with CKD when using $eGFR_{Cr}$.[3] KDIGO noted that a 2013 meta-analysis of 90,000 individuals found that with a Cr-based eGFR of 45 to 59 mL/min/1.73 m^2 (42%) had a CysC-based eGFR of ≥ 60 mL/min/1.73 m^2. An $eGFR_{Cr}$ of 45 to 59 represents 54% of all patients with CKD, amounting to millions of people (including current and former military personnel).[3,29-31] Correcting a misdiagnosis of CKD would bring significant relief to patients and save millions in health care spending.

CONCLUSIONS

In patients who meet CKD criteria using $eGFR_{Cr}$ but without other features of CKD, we recommend using confirmatory CysC levels and the $eGFR_{Cr\text{-}Cys}$ equation. This will align care with the KDIGO guidelines and could be a cost-effective step toward improving military patient care. Further work in this area should focus on determining the knowledge gaps in primary care practitioners' understanding of the limits of $eGFR_{Cr}$, the potential mitigation of concomitant CysC testing in equivocal CKD cases, and the cost-effectiveness and increased utilization of CysC.

Author affiliations

[a]Family Medicine Residency, Eglin Air Force Base, Florida
[b]Department of Internal Medicine, University of Florida, Gainesville
[c]Carl T. Hayden Veterans Affairs Medical Center, Phoenix, Arizona

Author disclosures

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Ethics and consent

Verbal and written informed consent for publication was obtained from the patient. All identifying patient information has been removed to protect patient privacy.

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