National Kidney Foundation®

CYSTATIN C

WHAT IS ITS ROLE IN ESTIMATING GFR?

FOUR CURRENT QUESTIONS:

1. **Does cystatin C have the potential to make estimates of GFR more accurate?**
2. **Are estimating equations that use both creatinine and cystatin C more accurate than those that use only one of these?**
3. **What patient populations would most benefit from using cystatin C in GFR-estimating equations?**
4. **Will adjustments based on patient age, sex, race, or size be needed in cystatin C GFR-estimating equations?**

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Introduction

HOW IS KIDNEY FUNCTION DETERMINED?

The rate at which glomeruli in the kidney filter impurities in the blood is the glomerular filtration rate (GFR). GFR is defined as the volume of plasma that can be completely cleared of a particular substance by the kidneys in a unit of time.[2] There is no simple and practical way to measure GFR directly, so it is estimated. To estimate the GFR, an endogenous substance in the blood that is cleared by the kidney is used. This substance is currently serum creatinine, which is used to estimate GFR in equations that include age, race, and gender, so it can be adjusted to account for average differences in muscle mass among subgroups. The Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) Study equations are serum creatinine-based equations that are used to estimate GFR. GFR determinations by creatinine-based equations are not precise, so other substances, such as cystatin C, are being explored to estimate GFR. Cystatin C, a non-glycosylated 13 kDa protein, has the potential to improve estimates of GFR, because it is thought to be less influenced by muscle mass or diet.

KEY POINT

Accurate estimation of glomerular filtration rate (GFR) is essential for the diagnosis, staging, and management of chronic kidney disease (CKD).[1] Combining serum creatinine with cystatin C in a GFR estimating equation may provide a more accurate measure of true GFR than creatinine-based methods in adult and pediatric patients with CKD. More studies are required to see if this is true in those without CKD.

Why could cystatin C be a good marker of GFR?

CYSTATIN C HAS DESIRABLE TRAITS AS A MARKER OF GFR. IT IS THOUGHT TO BE:

- **Filtered solely by the glomerulus**
- **Not secreted by the renal tubules**
- **Completely reabsorbed by the tubules and then catabolized**
- **Generated at a constant rate by all cells in the body**

More information is needed, however, because the filtration properties of cystatin C are difficult to determine since it is not excreted in the urine. In addition, there are substantial differences among assays used to measure cystatin C. It is also important to note that serum creatinine is being standardized nationwide. This has not yet happened for cystatin C, although it is in progress.

GFR is needed to determine the stage of CKD and is used to determine the appropriate clinical action plan.

TWO META-ANALYSES HAVE CONCLUDED THAT SERUM CYSTATIN C IS SUPERIOR TO SERUM CREATININE AS A MARKER OF KIDNEY FUNCTION.[3,4]

However, recent findings suggest an equation that uses both serum creatinine and cystatin C with age, sex, and race would be better than equations that use only one of these serum markers. [5,6]

In May 2009, Levey et al[7] reported that the CKD-EPI creatinine equation was somewhat more precise than the MDRD Study equation, especially at higher GFRs. Using the new equation could decrease false-positive results, the team reported.

The "gold standard" for determining GFR is to measure the clearance of an exogenous substance such as inulin. However, the measurement of inulin is too time-consuming, labor-intensive, and expensive for routine monitoring.

WHAT ARE THE LIMITATIONS OF CREATININE-BASED GFR?

The primary limitation of creatinine is that levels are determined not only by GFR, but also by muscle mass and dietary intake. Lower serum creatinine levels may less reliably detect impaired GFR in patients with certain characteristics: older age, female sex, chronic illness with muscle wasting, amputation, or a vegetarian diet. Higher serum creatinine levels are associated with African American race, muscular body habitus, and a high-protein diet. While estimating equations attempt to adjust for these factors, the result is not precise. Different patients can have the same serum creatinine with very different GFR.

THE SAME SERUM CREATININE: VERY DIFFERENT eGFR*

**The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) currently recommends the use of estimated GFR (eGFR) based on serum creatinine and age, race, and gender. A result lower than 60 mL/min/1.73 m² for 3 months or more, or kidney damage for 3 months or more, defines CKD.*

22-YR-OLD BLACK MAN

58-YR-OLD WHITE MAN

80-YR-OLD WHITE WOMAN

	22-YR-OLD BLACK MAN	58-YR-OLD WHITE MAN	80-YR-OLD WHITE WOMAN
Serum creatinine	1.2 mg/dL	1.2 mg/dL	1.2 mg/dL
GFR as estimated by the MDRD equation	98 mL/min/1.73 m²	66 mL/min/1.73 m²	46 mL/min/1.73 m²
Kidney function	Normal GFR *or* stage 1 CKD if kidney damage is also present	Stage 2 CKD if kidney damage is also present	Stage 3 CKD

OTHER LIMITATIONS OF CREATININE-BASED eGFR

- **Acute changes in kidney function are not immediately apparent.**
- **Creatinine excretion is due not only to filtration (90%–95%) by the kidney but also to secretion (5%–10%) by the distal tubule. If the patient with advanced CKD takes a substance that blocks distal tubule secretion of creatinine (eg, trimethoprim, cimetidine, cefoxitin), the serum creatinine level will increase abruptly, but the actual GFR will not change.[8]**
- **Extra-renal elimination of creatinine occurs.**

Source: Stevens L, et al. *NEJM*. 2006;354:2473-2483.

KEY POINT

An equation that uses both serum creatinine and cystatin C with age, sex, and race may be better than equations that use only one of these serum markers.[5]

WHAT IS THE ROLE OF CYSTATIN C IN ESTIMATING GFR?

Research is underway studying various GFR estimating equations. Some use cystatin C alone, others add cystatin C to creatinine; still others add age, race, and sex, with or without creatinine. It will take more research to find out which of the many potential equations gives the most accurate GFR estimate.

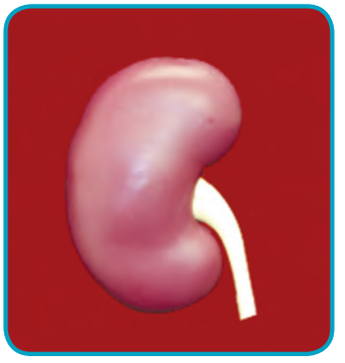
Twenty-nine studies (21 in adults) reported before 2009 compared serum creatinine with cystatin C in CKD patients. Of those, 17 showed cystatin C was a better predictor of GFR, while 12 showed no difference in the prediction of GFR.[9] Until larger-scale studies and well-designed trials exist that demonstrate that cystatin C is a superior marker of GFR, using it in combination or in addition to serum creatinine may be advisable.

Some differences could be clinically important. A study comparing a cystatin C formula to creatinine-based formulas showed cystatin C was more likely to correctly predict that the patient's GFR was below or above 60 mL/min/1.73 m^2 than the MDRD formula using creatinine (91.6% versus 84.1%, $P<0.0005$).[10] However, both equations alone underestimated the measured GFR and lacked precision. For the same level of eGFR, serum cystatin levels were 9% lower for women than men, 6% higher for blacks than for whites, and 9% lower for 40-year-olds compared to 20-year-olds.

The addition of age, sex, and race to cystatin C helps make it more accurate, but combining these factors with serum creatinine may provide the best estimation of GFR. In a recent study by Stevens, et al, an equation that used both serum creatinine and cystatin C with age, sex, and race was better than equations that use only one of these markers.[5]

HOW IS CYSTATIN C MEASURED?

New immunoassay methods from several different manufacturers measure cystatin C and this has made it more practical and clinically useful to estimate GFR. These methods are automated and results are rapidly available. Standardization of testing by clinical laboratories will be important to derive accurate GFR estimates.[11]



USING CYSTATIN C

CLINICAL CONSIDERATIONS WITH VARYING DEGREES OF KIDNEY FUNCTION

Early Kidney Disease

According to early reports, cystatin C may detect mild-to-moderate decreases in GFR that are not evident with serum creatinine-based measurements. Some studies suggest that CysC–GFR was better than creatinine-based estimates of GFR at GFR levels >60 mL/min/1.73 m^2 (CKD stages 1 and 2).[42] In addition, CysC–GFR appeared to be better correlated with microalbuminuria, while MDRD and CG creatinine estimates of GFR tend to reflect only proteinuria.[43] Using CysC–GFR, over one-third of type 1 diabetes patients with microalbuminuria at the time of enrollment already had evidence of mild (CysC–GFR <90) or moderate (CysC–GFR <60 mL/min/1.73 m^2) CKD.[44]

Kidney Transplantation

CysC–GFR after transplant has been used to detect allograft rejection and monitor drug nephrotoxicity, with reported diagnostic value.[45] In kidney transplant patients, cystatin C was reported to be more sensitive than serum creatinine for detecting decreases in GFR and delayed graft function, offering an opportunity for timely intervention.[46] Follow-up studies have found GFR was overestimated 30% when derived from plasma creatinine levels.[47] Even though cystatin C underestimated GFR by 14%, it was still more sensitive in detecting kidney damage, with no false-negative results. Note also, though, that routine or rejection-necessitated treatment with corticosteroids led to a significantly increased serum cystatin C concentration.[48]

Acute Kidney Injury (AKI)

Serum cystatin C has been reported to outperform conventional biomarkers in the prediction of AKI and to have prognostic value of the need for kidney transplant and in-hospital mortality.[49] Cystatin C has been reported to increase about one to two days earlier than serum creatinine in patients developing AKI.[50] AKI is not rare in hospitalized patients, with a mortality rate estimated to be between 30% and 90%.

TABLE 1. CHRONIC KIDNEY DISEASE: CLASSIFICATION BY SEVERITY[50]

STAGE	DESCRIPTION	GFR (mL/min/1.73 m^2)	RELATED TERMS	CLASSIFICATION BY TREATMENT
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, hematuria	T if kidney transplant recipient
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria, hematuria	
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, early renal insufficiency	
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD	
5	Kidney Failure	<15 (or dialysis)	Renal failure, uremia, end-stage renal disease	D if dialysis (hemodialysis or peritoneal dialysis)

Abbreviations: *GFR, glomerular filtration rate; ESRD, end-stage renal disease*

Related terms for CKD stages 3 to 5 do not have specific definitions, except ESRD.

Source: Levey AS, et al. *Kidney Intl.* 2005;67:2089-2100.[51]

HOW IS GFR ESTIMATED?

CREATININE EQUATIONS

1. The original MDRD Study equation[12,13]:

$$eGFR = 186 \times SCr^{-1.154} \times age^{-0.203} \times 1.212 \text{ (if African American)} \times 0.742 \text{ (if female)}$$

2. The "reexpressed" MDRD Study equation for standardized SCr[14]:

$$eGFR = 175 \times \text{standard } SCr^{-1.154} \times age^{-0.203} \times 1.212 \text{ (if African American)} \times 0.742 \text{ (if female)}$$

CYSTATIN C EQUATIONS

3. CKD-EPI cystatin equation not adjusted for age, sex, and race[14]:

$$eGFR = 76.7 \times CysC^{-1.19}$$

4. CKD-EPI cystatin equation adjusted for age, sex, and race[14]:

$$eGFR = 127.7 \times CysC^{-1.17} \times age^{-0.13} \times 0.91 \text{ (if female)} \times 1.06 \text{ (if African American)}$$

5. CKD-EPI cystatin and creatinine equation adjusted for age, sex, and race[15]:

$$eGFR = 177.6 \times SCr^{-0.65} \times CysC^{-0.57} \times age^{-0.20} \times 0.80 \text{ (if female)} \times 1.11 \text{ (if African American)}$$

Note: GFR is expressed as mL/min/1.73 m^2; Age is expressed in years; weight is expressed in kilograms.

Conversion factors for units: GFR in mL/min/1.73 m^2 to mL/s/1.73 m^2, × 0.01667; SCr in mg/dL to µmol/L, x 88.4; serum CysC in mg/L to nmol/L, × 74.9.

Abbreviations: *CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CysC, serum cystatin C; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; SCr, serum creatinine*

Source: Stevens LA, Levey AS. *Am J Kid Dis*. 2009;53:S17-S26.

KEY POINT

There are many formulae that can be used to estimate GFR. Currently, the question of which is most precise and clinically valuable is being studied.

GUIDANCE FOR COMPARING GFR-PREDICTING EQUATIONS

KEY POINT

Additional experience will be needed to determine the bias, precision, and accuracy of cystatin C-based GFR estimates.

In 2002, the National Kidney Foundation released clinical guidelines on the evaluation of CKD and proposed a methodological framework to evaluate GFR-predicting equations according to "bias," "precision,"and "accuracy." "Bias" expresses the systematic deviation from the gold standard measure of GFR and is given by the difference between the true and estimated values of GFR (absolute bias). Clinically this is relevant at lower GFRs, as there is less concern about the difference between 100 and 130 mL/min/1.73 m^2 than between 30 and 60 mL/min/1.73 m^2. "Precision" expresses the variability (or dispersion) of predictions around the true GFR and corresponds to the standard deviation of the difference between the true and estimated GFR. This considers the reproducibility of the result. "Accuracy" combines precision and bias and is measured by the proportion of estimates falling within a certain percent of the true GFR (eg, 30% accuracy is the proportion of predicted GFR within ±30% of the true GFR). "Bias," "precision," and "accuracy," as defined by the National Kidney Foundation, are simple and reproducible criteria. It refers to how close the measurement is to a traceable or standard value.

USING CYSTATIN C: CLINICAL CONSIDERATIONS WITH CERTAIN DIAGNOSES

Diabetes and HIV

Diabetes: Cystatin C has been reported to be a reliable marker of GFR in patients with mild-to-moderate impairment of kidney function (stages 2–3 of CKD) in both type 1 and type 2 diabetes,[24] although the studies reporting this are of varying quality.[25-27] Elevated serum cystatin C levels have also recently been identified as a significant prognostic indicator for the development of cardiovascular disease in people with diabetes. Hoek et al[28] reported that not only was cystatin C a better indicator of GFR than creatinine in people with diabetes, it was the parameter which had the best correlation (r = 0.66) with changes in GFR over two years, making it a useful measure for follow-up of patients with diabetes.

HIV: More research is needed, since cystatin C is increased with HIV, but creatinine-based estimates of GFR have not been tested rigorously in HIV-infected persons. This population is known to be influenced by malnutrition, wasting syndrome, and anabolic steroid treatment.[29] Because of an increase of cystatin C levels with active HIV infection, an overestimation of kidney impairment may occur, particularly in treatment-naive patients.[30]

Thyroid Function, Hepatic Disease

In contrast to creatinine concentrations, cystatin C levels are lower in the hypothyroid and higher in the hyperthyroid state as compared with the euthyroid state.[31]

Liver disease affects the reliability of creatinine-based GFR measurements, but there are reports that CysC–GFR may be useful in cirrhotic patients,[32] pediatric patients with chronic liver disease before and after liver transplantation[33] and in adults following liver transplantation.[34,35]

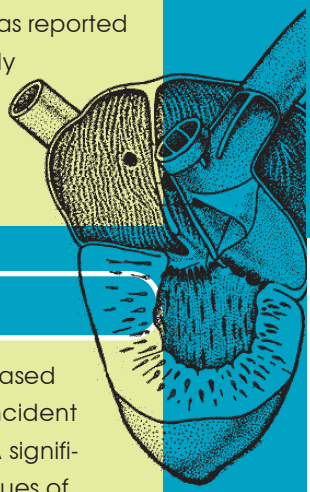
PRELIMINARY FINDINGS ABOUT CYSTATIN C eGFR IN VARIOUS PATIENT POPULATIONS

Prediabetes

Diabetic nephropathy is likely to be more susceptible to intervention at early stages. Early kidney impairment indexed with cystatin C imparted a three-fold excess risk of progression to prediabetes in 1,455 subjects free of type 2 diabetes and known cardiovascular disease at baseline (1996–2001), who were re-examined in 2002–2004.[36]

Cardiovascular Disease

Cystatin C has been reported to be a potent predictor of cardiovascular mortality beyond classical risk factors in patients with CAD and normal or mildly reduced kidney function.[37] Serum cystatin C may have a stronger association with mortality and cardiovascular disease than serum creatinine in patients without CKD, as reported in a large study of older adults.[38]



Prediction of Adverse Events

High cystatin C concentrations predict substantial increased risks of all-cause mortality, cardiovascular events, and incident heart failure among ambulatory persons with CHD.[39,40] A significant increase in the risk of death was observed with values of cystatin C that were as low as 1.0 to 1.1 mg/L (corresponding to an estimated GFR of 72±12 mL/min/1.73 m^2). In contrast, risks were significantly increased only for the highest levels of serum creatinine (ie, 1.26 mg per deciliter for men and 0.96 mg per deciliter for women) and for the lowest levels of estimated GFR (ie, <56 mL/min/1.73 m^2).[41]

USING CYSTATIN C: CLINICAL CONSIDERATIONS IN VARIOUS PATIENT GROUPS

Pediatrics

After age 1, serum cystatin C concentration is constant, but higher values are found in the newborn period. In full-term newborns, cystatin C progressively declines over the first week of life, and less significantly, over the first month.[16] CysC–GFR has been reported to be more accurate in children with cancer[17] and in patients with spina bifida or spinal injury.[18] After age 1, body mass exerts a minimal effect on CysC–GFR estimation, but height and gender influence it.[19] See an estimating equation below.

Adolescents

Adjustment of GFR estimates for gender and height and other variables may be necessary (see the cKiD estimating formula below). In adolescents, serum cystatin C is significantly affected by gender, age, race/ethnicity, uric acid, and blood urea nitrogen.[21]

PATIENT CHARACTERISTICS AND CYSTATIN C RESEARCH

Seniors

GFR declines with age and cystatin C may better reflect true kidney function in older people because muscle mass does not influence it.[22] After age 50, reference values of serum cystatin C concentration are higher. The prevalence of stage 3 CKD in an elderly population when GFR is estimated by the MDRD Study equation, is significantly higher than the prevalence obtained when CysC–GFR equations are used.[23]

Obstetrics

Serum cystatin C concentration varies in pregnancy, because it is not consistently produced. In preeclampsia, however, altered kidney function is more likely to be detected by CysC–GFR than by creatinine-based formulas.[20]

AN ESTIMATING EQUATION IN CHILDREN

$$GFR(mL/min\ per\ 1.73\ m^2) = 39.1[height\ (m)/Scr\ (mg/dl)]^{0.516} \times [1.8/cystatin\ C\ (mg/L)]^{0.294} [30/BUN\ (mg/dl)]^{0.169} [1.099]^{male} [height\ (m)/1.4]^{0.188}$$

GFR ESTIMATION IN CHILDREN: THE CKID STUDY

The most precise equation for estimating GFR in children uses cystatin C, BUN and serum creatinine plus height and gender, according to the Cohort Study of Chronic Kidney Disease in Children (cKiD), an ongoing multicenter, prospective study.[6] This formula yielded 87.7% of estimated GFR within 30% of the iohexol-GFR (iGFR), and 45.6% within 10%.

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