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# The estimated glomerular filtration rate as a test for chronic kidney disease: Problems and solutions

**A**T THE AMERICAN SOCIETY of Nephrology Renal Week 2010, one of the authors (A.D.R.) presented the following question at an In-Depth Nephrology Course on Geriatric Nephrology:

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A 65-year-old woman donated a kidney to her son. Before donation, her serum creatinine level was 1.0 mg/dL, her estimated glomerular filtration rate (GFR) was 56 mL/min/1.73 m<sup>2</sup>, and her measured GFR was 82 mL/min/1.73 m<sup>2</sup>, which was below the 2.5th percentile for 20-year-old potential kidney donors. The patient had no albuminuria or hypertension and was otherwise healthy. The kidney was biopsied during the transplant surgery. The biopsy revealed 2 of 20 glomeruli as globally sclerosed, a focus of tubular atrophy, and mild arteriosclerosis (findings present in less than 2.5% of 20-year-old donors).

Choose one. Prior to donation, this woman had:

- Chronic kidney disease (CKD), and she should not have donated her kidney
- CKD, but kidney donation was reasonable
- Age-related (senescent) changes in her kidneys, and should not have donated her kidney
- Age-related (senescent) changes in her kidneys, but kidney donation was reasonable

Using an electronic response system, 36 (82%) of 44 physicians in the audience chose the last option, even though this patient meets the current definition of CKD (an estimated GFR less than 60 mL/min/1.73 m<sup>2</sup>) and has chronic parenchymal damage documented by a kidney biopsy.

## ■ PROBLEMS WITH THE GFR AND CKD CLASSIFICATION

This question highlights several key problems with the GFR and CKD classification.

First, in low-risk populations such as potential kidney donors, serum-creatinine-based equations such as the Modification of Diet in Renal Disease (MDRD) equation and the Chronic Kidney Disease Epidemiology Study (CKD-EPI) equation substantially underestimate the GFR.<sup>1</sup>

Second, many healthy older adults with normal serum creatinine levels have an estimated GFR and a measured GFR below the normal range for young adults.<sup>2</sup>

Third, many healthy older adults have evidence of chronic parenchymal damage on renal biopsy, unlike healthy young adults.<sup>3</sup>

Finally, many health care providers did not previously recognize that people with a normal serum creatinine level could have a reduced GFR, and widespread use of the estimated GFR has addressed this problem. However, many physicians remain skeptical about efforts this past decade to classify age-related changes in kidney function as a “disease” in the absence of a clear benefit to older patients.<sup>4</sup>

**Creatinine-based testing is not perfect; perhaps a two-step approach would be better**

doi:10.3949/cjcm.78a.11004

## ■ TWO POINTS ABOUT THE ESTIMATED GFR

In this issue of the *Cleveland Clinic Journal of Medicine*, Simon and colleagues<sup>5</sup> provide a balanced assessment of the benefits and pitfalls of using the estimated GFR in clinical practice. Two points they make deserve further discussion:

**Bigger people make more creatinine.** GFR can be reported in units of milliliters per minute, or in units normalized to body surface area (mL/min/1.73 m<sup>2</sup>). Contemporary equations for identifying and classifying CKD use the latter, because the GFR is considered inappropriately low when metabolic waste is not being adequately cleared. It is intuitive that smaller people require less absolute GFR than larger people, who generate more metabolic waste. Indexing GFR to 1.73 m<sup>2</sup> assumes that body surface area is a good surrogate for metabolic waste generation. However, whether body surface area is the *best* surrogate for the rate of metabolic waste generation has long been a subject of debate.<sup>6</sup>

**The relationship between GFR and serum creatinine is not linear.** Due to the inverse relationship between serum creatinine and GFR, a small change in serum creatinine from 0.9 to 1.2 mg/dL will represent a relatively large change in GFR (eg, 85 to 65 mL/min/1.73 m<sup>2</sup>), whereas a large change in serum creatinine from 5 to 9 mg/dL will represent a smaller change in GFR (eg, 10 to 5 mL/min/1.73 m<sup>2</sup>). The latter may be of great concern since it represents a fall in GFR to levels at which dialysis is likely needed. With the former, subtle changes in serum creatinine represent large changes in GFR, but there is also much more day-to-day variability in GFR in the normal or near-normal range than in the advanced range of kidney disease. This is one of the reasons the MDRD and CKD-EPI equations were developed, using logarithmic models that emphasize percentage instead of absolute differences in GFR.

## ■ BEYOND CREATININE?

As Simon and colleagues point out,<sup>5</sup> although serum creatinine is a flawed surrogate for GFR, there are many problems with determining GFR by other means.

Direct GFR measurement relies on the use of an exogenous marker such as inulin or iothalamate that is infused or injected, followed by timed urine and plasma measurements to calculate GFR by the urinary clearance method (UV/P, where U is the concentration of the marker in the urine, V is the urine volume, and P is the concentration of the marker in the plasma). Alternatively, timed plasma measurements of the marker alone can be used to determine GFR by the plasma clearance method. The problem is that direct GFR measurement is costly, invasive, imprecise, time-consuming, and impractical in most clinical settings.

Exogenous markers for determining GFR are chosen because they are metabolically inert, are cleared by glomerular filtration without tubular secretion or reabsorption, and have no extrarenal clearance via the liver or intestines. Endogenous markers such as serum creatinine do not fulfill all of these ideal criteria.

Simon and colleagues highlight the problem of using the estimated GFR to screen for CKD in populations of ostensibly healthy persons.<sup>5</sup> The MDRD and CKD-EPI equations contain demographic variables to approximate the creatinine generation rate. The primary source of creatinine generation is muscle, and the coefficients in these equations reflect the higher muscle mass of younger individuals, males, and African Americans. However, any creatinine-based equation is fundamentally flawed because overall health also affects muscle mass: healthy people have greater muscle mass than people with chronic illness, including those with CKD. Therefore, at the same serum creatinine level, a healthy person has a higher GFR than a patient with CKD.<sup>1,7</sup> This problem leads to circular reasoning, since you need to know whether the patient has CKD or is healthy in order to accurately estimate GFR, but estimated GFR is being used to determine whether the patient is healthy or has CKD.

Therefore, other endogenous markers that are also eliminated via glomerular filtration, such as cystatin C, have been used to construct equations that estimate GFR. Unfortunately, factors other than GFR, such as inflammation, can also influence blood cystatin C levels. This in turn impairs the accuracy of

**Many physicians remain skeptical about calling age-related changes in kidney function a 'disease'**

equations that use cystatin C to estimate GFR in the general population.<sup>8</sup> No known endogenous marker of GFR can be used in all patients without any confounding factors.

To rectify this problem, recent studies have investigated the use of a confirmatory test to determine which patients with a creatinine-based estimated GFR less than 60 mL/min/1.73 m<sup>2</sup> actually have kidney disease or have a false-positive result due to higher-than-average creatinine generation. Both albuminuria and elevated serum cystatin C are examples of useful confirmatory tests that sub-

stantially decrease the misdiagnosis of CKD in healthy adults with an estimated GFR less than 60 mL/min/1.73 m<sup>2</sup>.<sup>9,10</sup>

Imagine if we identified and staged systemic lupus erythematosus on the basis of antinuclear antibody levels alone: this would parallel the current approach that largely uses serum creatinine alone to classify CKD. Confirmatory tests and considering patient-specific risk factors could avoid potential harm to healthy individuals and yet retain gains that have been made to improve the interpretation of serum creatinine levels in CKD patients. ■

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