Looking for a Better Creatinine

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Our kidneys maintain a constant internal environment and circulatory volume through a combination of filtration, selective reabsorption and secretion, and production of several key hormones. Young, healthy individuals filter >100 L of blood each day; however, their kidneys then reabsorb most of this for a mean urine output of only 1.5 L/day. This filtration process is necessary to eliminate byproducts of ongoing metabolism (so-called uremic toxins). Indeed, a minimum amount of kidney function is essential for life, and one can demonstrate increased morbidity and mortality when the glomerular filtration rate (GFR) chronically dips low enough. Thus, GFR is widely considered the single most important and useful indicator of overall kidney function.

It is possible to directly measure GFR by administration of small molecules that are freely filtered by the kidneys and neither metabolized, secreted, nor reabsorbed. Examples include inulin, iohalate, and iohexol, for which the renal clearance of these molecules equals GFR. However, protocols that use these exogenous agents to measure GFR require some combination of intravenous or subcutaneous administration of the marker, multiple blood draws, and carefully timed urine collections. Thus, direct measurement of GFR is not practical for most routine situations.

For these reasons, several methods of GFR estimation have been developed on the basis of endogenous molecules. The best example is creatinine, a byproduct of muscle metabolism that is freely filtered, produced in a relatively consistent manner, and not reabsorbed. Although some creatinine is secreted, this amount is usually small enough that creatinine remains a useful marker of GFR. A bigger problem, however, is that muscle mass (and consequently serum creatinine) varies widely between individuals. Thus, although serum creatinine goes up as GFR goes down, the GFR for a given serum creatinine can vary widely between individuals. For example, a “normal” serum creatinine of 1.0 mg/dL (88 μmol/L) can reflect a GFR range of 20–150 mL·min⁻¹·(1.73 m²)⁻¹, depending on the individual’s age, sex, and ethnicity (Fig. 1).

In 1976, Cockcroft and Gault made a seminal observation in a cohort of men when they reported that 24-h creatinine production varied in a predictable way with age and weight (1). This work yielded the Cockcroft–Gault equation, still widely used today. Although this equation is a helpful tool, certainly better than use of serum creatinine alone, the Cockcroft–Gault equation yields only an estimate of creatinine clearance and not GFR. In 1999, Levey and colleagues took another seminal leap forward by relating GFR to serum creatinine and demographic factors (2). Within the large population of patients with previously diagnosed chronic kidney disease (CKD) that were studied, sex, race, and age were the most important variables that influenced serum creatinine correlations with GFR measured by iohalate clearance. Hence, these variables were incorporated into the first estimated GFR (eGFR) tool, the widely used Modification of Diet in Renal Disease (MDRD) equation.

Although the MDRD equation works very well for patients with CKD, the population in whom it was developed, it works less well for other groups. In particular, the MDRD equation underestimates GFR in healthy individuals (3). Therefore, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was subsequently developed by use of a mixed population of individuals with (approximately 70%) and without (approximately 30%) CKD. In general, the CKD-EPI equation does estimate GFR more accurately in healthy individuals, albeit at the expense of some loss in accuracy for those with CKD.

The Achilles heel of any creatinine-based GFR estimate is the influence of muscle mass on creatinine production. Consequently, a search for alternative serum markers of GFR has gained increasing momentum. Cystatin C is a 13-kDa cysteine protease inhibitor produced at a constant rate by most nucleated cells. Because cystatin C is freely filtered into the urine, it has attracted great attention as a potential serum marker of GFR. Indeed, serum cystatin C concentrations have a much tighter relationship with measured GFR than serum creatinine (Fig. 1). Perhaps most importantly, cystatin C outperforms creatinine as an indicator of GFR in the...
clinically relevant range of 30–90 mL min \(^{-1}\) (1.73 m\(^2\))\(^{-1}\) that spans CKD stages 3–4. Fig. 1 shows that, if no other demographic information were available, serum cystatin C would better reflect GFR than creatinine alone. Indeed, work over the last decade has in many ways validated this use of cystatin C as an indicator of kidney function, but also pointed out some interesting nuances. Three papers in the New England Journal of Medicine highlight these issues.

In 2005, Shlipak and colleagues first highlighted the prognostic value of cystatin C (4). Among 4637 participants ≥65 years of age in the prospective Cardiovascular Health Study, serum cystatin C concentrations were a strong predictor of both cardiovascular and overall mortality. Those in the highest quintile had an adjusted all-cause mortality risk of 1.77–2.58 compared to those in the lowest quintile. In contrast, relationships of mortality risk with creatinine or creatinine-based estimated GFR by quintile were weaker (1.00–1.48 and 1.21–1.78, respectively), and also J-shaped (those in the lowest quintile had a higher risk of death). Furthermore, within each quintile of creatinine the risk of death could be stratified based on cystatin C concentration (4). Thus, cystatin C seemed to impart additional and important prognostic information above and beyond creatinine. As the authors noted, other cardiovascular risk factors also correlated with cystatin C, such as C-reactive protein, HDL cholesterol, and waist-to-hip ratio. Because adipocytes are known to produce large amounts of cystatin C, it could well be that its serum concentrations integrate several signals that impact risk in addition to kidney function.

As noted above, the use of equations that include demographics has revolutionized our ability to use serum creatinine to estimate GFR. In an analogous fashion, equations have been developed to estimate GFR
from cystatin C. Because serum cystatin C is fairly tightly associated with GFR (Fig. 1), equations that include only cystatin C perform reasonably well. Nevertheless, the addition of demographics further improves the ability of cystatin C to estimate GFR. Recently, Inker and colleagues developed and compared the performance of equations that include cystatin C alone or creatinine plus cystatin C to estimate GFR (5). The study cohort included >6000 participants with and without CKD and excluded any transplant recipients. In general, the cystatin C equation had accuracy and precision similar to the creatinine-based equation. Thus, the use of demographics has greatly evened the playing field between the 2 biomarkers. However, the combined equation outperformed either of the single biomarker equations. This interesting observation may reflect the fact that each biomarker alone has its own set of confounders, so that averaging the 2 together in a single equation gives the best reflection of GFR, the parameter the equations are trying to capture. The authors demonstrated 1 potential use of the combined equation that has since been adopted in the 2012 Kidney Disease/Improving Global Outcomes (KDIGO) guidelines. Among participants with a creatinine-based GFR estimated between 45 and 74 mL \( \cdot \) min\(^{-1} \cdot \) (1.73 m\(^2\))\(^{-1} \) (just above and below the CKD stage 3 cutoff value of 60 mL \( \cdot \) min\(^{-1} \cdot \) (1.73 m\(^2\))\(^{-1} \)), cystatin C–based or the combined equation reclassified about 20% of this subgroup, and two thirds of these were moved into the correct CKD class.

Another very recent paper by Shlipak and colleagues returned to the prognostic value of cystatin C, in this case using the newly derived equations for estimating GFR (6). They performed a metaanalysis of data from >90 000 participants in 11 general population and 5 CKD cohorts. As before (4), cystatin C measurements were more strongly associated with risk of all-cause mortality compared with creatinine. Additionally, reclassification of creatinine-estimated CKD stage by cystatin C eGFR improved outcome prediction at any CKD stage. Thus, patients with higher cystatin C compared with creatinine eGFR had reduced risk, and those with lower cystatin C compared with creatinine eGFR had higher risk. There was no gold standard measure of GFR available in the metaanalysis, so we do not know if the superior prognostic value of cystatin C is related to a better approximation of GFR or instead reflects other confounding factors (e.g., obesity, inflammation, and diabetes).

Where does this leave us? By use of the current generation of equations (5), creatinine and cystatin C are roughly equivalent for estimating GFR. Because creatinine is more widely available, is much cheaper, and has a much greater clinical familiarity, it is likely to be the routine biomarker of renal function for the foreseeable future. In addition, current creatinine assays are better standardized, with traceability to isotope dilution mass spectrometry. However, cystatin C has important features that make it useful in certain clinical situations. Specifically, because cystatin C is not affected by muscle metabolism, it provides a more reliable estimate of GFR among individuals with abnormal muscle mass (e.g., very elderly or malnourished individuals). Cystatin C also provides an advantage for risk stratification. This is an important feature, since measurement of cystatin C among patients with CKD established by creatinine-based eGFR equations, or in patients at high risk of CKD, could identify those persons at greatest risk of adverse outcomes. Simultaneously, those persons with a cystatin C eGFR higher than the creatinine-based values appear to have a better prognosis and might not require as intensive follow-up. In any case, current data support prospective validation of management strategies that use cystatin C and an expanding role for this analyte in routine practice.

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References