Measured GFR as "Gold Standard"—All that Glitters Is Not Gold?

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Clin J Am Soc Nephrol 6: 1813–1814, 2011. doi: 10.2215/CJN.06040611

Glomerular filtration rate (GFR) is the parameter that has been used most commonly as the "overall index" of renal function. Historically, inulin has been considered the ideal filtration marker used to determine GFR. The classic procedure for measuring inulin clearance is rigorous and includes a continuous intravenous infusion, multiple repeat blood and urine collections, and careful timing of blood sampling.

Because such direct measurement of GFR is cumbersome and invasive, it is not practical for day-to-day clinical practice. As a result, numerous equations to estimate GFR have been developed. The oldest equation is the Cockcroft–Gault equation (3), which actually estimates creatinine clearance rather than GFR. In 1999, the first description of what became known as the six-variable Modification of Diet in Renal Disease (MDRD) study equation was published (4). This was followed by the "abbreviated" four-variable MDRD equation, which revolutionized the field (5). It was widely adopted in research studies and changed clinical practice by becoming the foundation for the widespread automatic reporting of estimated GFR (eGFR) whenever serum creatinine measurements are ordered (6). The next major advance in the application of GFR estimating equations was standardized calibration of serum creatinine measurements across laboratories (7). Even after calibration, the MDRD equation has been observed to give lower readings compared with directly measured GFR at higher GFR levels (8–10). To overcome this limitation and to base the GFR estimating equation on a more diverse population, the same research group recently developed the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (11).

The study by Murata *et al.* (12) in this issue of *CJASN* compared the accuracy of the MDRD and the CKD-EPI equations for estimating GFR in a large, diverse population with and without chronic kidney disease (CKD). The study included 5238 patients who underwent simultaneous outpatient serum creatinine and renal iothalamate clearance measurements. Clinical indications for the measurements included potential kidney donor, postnephrectomy kidney donors, native CKD, kidney transplant recipients, and non-kidney transplant recipients. The authors concluded that, overall, the MDRD equation was less biased for those with native CKD, kidney transplant recipients and other organ recipients. The CKD-EPI equation was less biased overall for potential kidney donors and postnephrectomy donors.

There have been many past—and there likely will be many future—studies evaluating the performance of eGFR compared with directly measured GFR. The assumption behind all of these studies is that it is clinically important for the eGFR to match the measured GFR. The assumption that the measured GFR is the "gold standard" is so commonly made that it is not explicitly acknowledged, but perhaps this should be reconsidered for several reasons.

First is that there are numerous ways to measure GFR directly, and these different methods often yield measurements that do not agree with each other. For example, examination of the Bland–Altman plot of an oft-cited study of nonradioactive iohexol (plasma) *versus* inulin (urinary) clearance suggested that the two readings often disagreed by as much as 20% (13). Another study showed that among patients with preserved GFR, iothalamate-measured GFR was approximately 20 ml/min per 1.73 m^2 higher than inulin-measured GFR (127.1 ± 12.4 *versus* 108.3 ± 14.1 ml/min per 1.73 m^2) (14). In the literature, any direct measure of GFR is typically taken to be the gold standard, without much attention paid to the details of the methodology. For example, in the study by Murata *et al.* (12), measured GFR was determined by using a single-period urine and plasma measurement, which may limit the accuracy of the measurement. In contrast, research studies have often used multiple-period measures to reduce the impact of errors in timing of blood and urine sampling.

Second, even if the same method is used, direct measures of GFR may not agree with each other when repeated. For example, one analysis of the MDRD and African American Study of Kidney Disease and Hypertension (AASK) studies found that measured GFR, as determined by the urinary clearance of ^{125}-I iothalamate, had substantial variability across visits within the same individual. When repeated on average 62 days apart, 8.0% of the second measured GFR gave results >30% different from the first measured GFR (15). Data such as these make untenable the belief that any single measurement of GFR represents "the true" renal function.

Third, measured GFR has not been shown to be

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better than other markers of kidney disease at predicting outcomes associated with poor kidney function. In a study comparing the strengths of association among four measures of renal function (1/serum creatinine, 1/serum cystatin C, MDRD equation eGFR, and iothalamate measured GFR) and four outcomes (all-cause mortality, cardiovascular disease mortality, kidney failure, and a composite outcome of kidney failure and all-cause mortality), measured GFR was not the strongest predictor in any of the four outcomes. For cardiovascular disease mortality, the adjusted hazard ratio (per 1-SD decrease) for measured GFR was 1.28 (95% confidence interval [CI] 1.04 to 1.59) but 1.64 (95% CI 1.28 to 2.08) for 1/cystatin C. In adjusted models for kidney failure, the hazard ratio for measured GFR was 2.41 (95% CI 2.15 to 2.70) compared with 2.81 (95% CI 2.48 to 3.18) for 1/creatinine (16). In addition, a recent cross-sectional study showed that measured GFR was not consistently superior to either creatinine-based or cystatin C–based eGFR in explaining comorbidities related to renal disease (*e.g.*, anemia, hyperkalemia, metabolic acidosis, and hyperphosphatemia) (17).

The exact reasons for the disappointing performance of measured GFR are not known but may be related to the fact that direct measures of GFR quantify renal function over a relatively short period, typically only several hours. Known variations in GFR are associated with time of day, posture, and diet (17–21). Estimates of renal function using endogenous filtration markers such as creatinine may provide a better measure of average renal function over a period of days to weeks, which is conceptually the underlying physiologic parameter of interest (22). Furthermore, measured GFR is subject to unique sources of measurement errors related to the timing of collection of urine and blood samples (17).

To conclude, investigations regarding estimating and measuring GFR have recently occupied much time and attention of many in academic nephrology. We believe that it is time for a general reassessment of these efforts. The principal clinical purpose of assessing a patient's renal function is to anticipate complications, enabling better screening and treatment decisions. Determining with great accuracy a certain physiologic parameter—actual GFR—is a less important goal.

Disclosures

None.

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See related article, "Relative Performance of the MDRD and CKD-EPI Equations for Estimating Glomerular Filtration Rate among Patients with Varied Clinical Presentations," on pages 1963–1972.