Improving the Clinical Value of Estimating Glomerular Filtration Rate by Reporting All Values: A Contrarian Viewpoint

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Abstract

The serious limitations of the estimating glomerular filtration rate (eGFR) appear related not to a shortcoming of the equation, but to the futility of trying to force agreement between two inherently different parameters: a blood marker of kidney function with a very stable concentration (creatinine) and a renal filtration parameter that fluctuates continually (glomerular filtration rate, GFR). Although GFR is regarded as the ultimate determinant of kidney function, it may be less ideal as an early clinical marker to detect declining kidney function. Another shortcoming of GFR is that it has significant overlap between health and kidney disease states categorized according to stage I, II, etc. Serum creatinine has a real and measurable increase as kidney function declines, but this is often masked when creatinine is plotted on a scale of 1.0 mg/dl (88 μmol/l), which is well above the detection limit of modern creatinine methods of about 0.05 mg/dl. A new equation to estimate GFR, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation, modestly improves accuracy from 80.6% of the Modification of Diet in Renal Disease (MDRD) eGFRs being within 30% of the measured GFR, to 84.1% of the CKD-EPI eGFRs being within 30% of the measured GFR. Creatinine methods have recently been standardized to an isotope dilution mass spectrometry reference method. While this will lessen the systematic bias between methods, it will have no effect on either the imprecision of a particular creatinine method or on the inherent random differences between serum creatinine (or eGFR) and actual GFR. Finally, the eGFR is not recommended for reporting until it is well below a reference range for those with no kidney disease. However, if the eGFR were properly regarded as an age-, gender-, and race-adjusted serum creatinine, it could be reported at all values and become a more clinically useful parameter.

Key Words
Renal function · Creatinine blood · Glomerular filtration rate · Cystatin C

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The glomerular filtration rate (GFR) is readily understood as an indicator of kidney function. However, because the measurement of actual GFR is not practical for routine clinical use, the Modification of Diet in Renal Disease (MDRD) equation for GFR, based on serum creatinine, age, gender, and race, for estimating GFR (eGFR) was developed. The intent was to provide a kidney function parameter that would lessen the likelihood of chronic kidney disease (CKD) going unnoticed by nonkidney specialists [1]. Numerous reports have shown the serious
limitations of the eGFR [2–5], most colorfully by Glassock and Winearls [2]. But are these really shortcomings of the equation used or are they futile attempts to force agreement between two inherently different parameters: an endogenous marker of kidney function with a very stable concentration in blood (creatinine) and a renal filtration measurement that fluctuates continually (GFR), even with normal kidney function?

Although GFR is regarded as the ultimate function of the kidney, it may be less ideal as a clinical marker to detect declining renal function. GFR is a dynamic parameter that changes as needed to regulate blood homeostasis and is also affected by diet and hemodynamic alterations [6]. In CKD, as nephrons are lost, the remaining nephrons compensate by hyperfiltration to maintain a near-normal GFR. Thus, this so-called ‘renal reserve’ maintains both GFR and serum creatinine levels during initial stages of chronic renal disease. While this is a frequent criticism of serum creatinine, GFR may be no better than serum creatinine as an early indicator of declining kidney function in CKD.

Another criticism of serum creatinine is that it is insensitive to early changes in kidney function. This belief is often based on a plot of serum creatinine (y-axis) versus diminishing GFR (x-axis) as a normal kidney function progresses to CKD, which gives the misleading visual illusion that serum creatinine changes minimally as GFR clearly declines from around 120 to around 60 ml/min [7, 8]. However, such plots mask a very real and measureable increase in serum creatinine by using a compacted y-axis scale of serum creatinine in increments of 1.0 mg/dl (88 μmol/l), which is well above the detection limit of modern automated methods for serum creatinine of about 0.05 mg/dl. If this data is plotted on a scale of 0.1 mg/dl, the increase in serum creatinine becomes readily apparent as GFR declines, as shown in figure 1. The increase in serum creatinine is also clearly evident in patients with polycystic kidney disease, as shown in a log-log plot of iohthalamate clearance versus serum creatinine in units of 0.1 mg/dl [9]. This report showed that the mean serum creatinine increased from about 0.5 to 1.0 mg/dl as iohthalamate clearance GFR decreased from 150 to 100 ml/min/1.73 m².

Cystatin C is another blood marker that increases as GFR decreases. A very recent article concluded that creatinine and cystatin C are each affected by factors other than GFR, with creatinine affected by factors related to muscle mass (age, gender, and race), and cystatin C affected by inflammation, obesity, and diabetes [10]. Like serum creatinine, cystatin C concentrations remained very stable in individuals without renal disease and did not correlate with creatinine clearance GFR measurements [11].

In addition, GFR by clearance measurements (creatinine, iohthalamate, or inulin) often do not agree well with each other [6] and especially do not agree with endogenous serum markers such as creatinine and cystatin C. While factors such as tubular secretion of creatinine, inaccuracy in urine collection, and both matrix effects and analytical variation on measurements of serum and urine are involved [12, 13], a major source of variation between GFR clearance measurements and either serum creatinine or eGFR values is that clearance measurements, especially from 1- to 4-hour urine collections, represent a snapshot of a process that varies continually, while serum creatinine (and eGFR) remains very stable over time [11]. Unfortunately, because values for eGFR and measured GFR differ most widely in the normal range, reporting ‘normal’ eGFRs was not recommended and only eGFR values ≤60 ml/min/1.73 m² were validated for reporting. While some claim this is adequate for early detection of CKD, a GFR <60 ml/min/1.73 m² might represent a significant loss of functional nephrons. These problems arise, however, because eGFR is trying to substitute for an actual GFR. Instead, if eGFR were correctly regarded as proportional to a serum creatinine that is adjusted or ‘normalized’ for age, gender and race, then all values of eGFR could be reported and compared to an appropriate (narrower) reference range. In this way, the eGFR would become a useful addition to all creatinine results.
Some believe that the problem with eGFR is in an imperfect eGFR calculation or that standardizing creatinine to an isotope dilution mass spectrometry (IDMS) method will improve the clinical utility [14]. However, the problem may lie with the measured GFR. GFR has a wide normal range of 72–140 ml/min/1.73 m², which overlaps with both stage 1 (>90 ml/min/1.73 m²) and stage 2 (60–89 ml/min/1.73 m²) CKD [7]. Thus the eGFR is trying to mimic a parameter (GFR) that has significant overlap between health and disease states. While the reference range for eGFR should be narrower than that for serum creatinine, the eGFR essentially has no reference range because only quantitative results ≤60 ml/min/1.73 m² are reported, which prevents its use for detecting early changes in renal function or for evaluating persons with normal renal function. Pottie and Martens [15] present a provocative report claiming that the MDRD eGFR adds little to a simple creatinine compared to appropriate reference intervals based on age for males and females. Furthermore, they show that the stages of kidney disease can be classified by the serum creatinine values as well as by the GFR. Using their data for males and females aged 50–54 years [table 1a, 15], the stages of CKD can be associated with appropriate ranges for serum creatinine (table 1).

This approach highlights the value of serum creatinine when it is compared to appropriate reference intervals for age and gender. On average, the serum creatinine for females is about 0.2 mg/dl lower than for males, giving reference ranges of 0.5–1.1 mg/dl for females and 0.7–1.3 mg/dl for males. In addition, serum creatinine declines gradually with age, approximately by 0.1–0.2 mg/dl every 5 years throughout adulthood [15]. Even though the eGFR uses ‘GFR’ in its name, it is actually proportional to a serum creatinine adjusted for age, gender, and race. If eGFR were correctly regarded as a serum creatinine normalized for age, gender, and race, it could be reported at all values and become more clinically useful and much easier to interpret than as a surrogate for GFR.

While serum creatinine appears to have a wide reference range, its reference range of approximately 0.6–1.3 mg/dl has about the same relative width as that for GFR (72–140 ml/min/1.73 m²) [16, 17], although GFR is rarely criticized for this shortcoming. While both serum creatinine and GFR by clearance measurements have relatively large and proportionately similar population variations [7, 18], the within-individual variation for serum creatinine is much lower than for GFR by creatinine clearance [11, 19], with iothalamate and inulin clearance measurements also having considerable variation [9, 20].

As expected, the eGFR (calculated from creatinine) correlates poorly with clearance measurements of GFR, either by creatinine, iothalamate or inulin clearance, especially in the normal range [7, 11, 20, 21]. While proposals to standardize creatinine methods to an IDMS method will minimally improve this variation, this effort misses the main point that differences between eGFR and measured GFR are largely due to inherently different physiologic regulation patterns between serum creatinine and GFR, which cannot be corrected by either an equation or universal agreement between creatinine methods. In an analogy to another set of laboratory tests, the GFR is like blood glucose, while the serum creatinine is like hemoglobin A1c.

As recommended for acute kidney injury [22], serial measurements of either serum creatinine or eGFR on the same individual should improve detection of changes in CKD. However, serial measurements may not be available in settings such as emergency medicine. When a single creatinine result must be interpreted relative to a population reference range, this might present a significant clinical opportunity for the eGFR (being a creatinine adjusted for age, gender, and race) to be interpreted with a narrower reference range. Again, the lack of a reference range for eGFR severely restricts its clinical use in such situations.

A report by Corsonello et al. [23] found that 16% of older patients with type 2 diabetes had normal serum creatinine (<1.2 mg/dl) and decreased MDRD eGFR (<60 ml/min). Although this report concluded that this group had ‘concealed renal failure’ and regarded the eGFR as a surrogate for the actual GFR, there was no direct measure of actual GFR on these diabetic patients.
by Rainey [14], the MDRD eGFR will often be <60 ml/min/1.73 m² while the actual GFR will be >60 ml/min/1.73 m². Furthermore, nephrologists commonly find the eGFR to be <60 ml/min/1.73 m² in elderly persons who have a serum creatinine that is stable at a slightly elevated level. Thus, the MDRD eGFR can give false positives in elderly patients who have a stable serum creatinine and no evidence of kidney disease.

A new equation to estimate GFR has recently been published by Levey et al. [24] as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. The authors claim it is more accurate than the older MDRD GFR equation, especially in the normal ranges. However, the improvement is modest, going from 80.6% of the MDRD eGFRs being within 30% of the measured GFR to 84.1% of the CKD-EPI eGFRs being within 30% of the measured GFR. This is also a reminder that the criterion of 30% for acceptable agreement between GFR and eGFR is very wide. One has to wonder why agreement within 30% is acceptable for eGFR, but a much smaller difference among serum creatinine methods required IDMS standardization.

If serum creatinine is related to but inherently different than GFR, then all equations for predicting GFR from creatinine, in addition to any systematic bias, will show random differences compared to measured GFR, especially in the early stages of declining kidney function. Although standardizing creatinine methods to an IDMS method will lessen the systematic bias between methods and improve agreement between creatinine results from different institutions, it will have no effect on either the imprecision of a particular creatinine method or the inherent random differences between serum creatinine (or eGFR) and actual GFR. Thus, if we properly regard the eGFR as an age-, gender-, and race-adjusted serum creatinine that could be interpreted relative to a single reference range for eGFR, then the eGFR could be reported at all values and become a useful parameter along with the serum creatinine. If a single eGFR were interpreted relative to its own reference range, the eGFR should have a narrower reference range than either unadjusted serum creatinine or GFR, and should better detect either chronic or acute changes in kidney function. Efforts could shift from the frustrating attempts to produce a GFR from a serum creatinine to simply redefining eGFR as an age-, gender-, and race-adjusted creatinine, and then refining a reference range for eGFR that is narrower than serum creatinine by factoring out the variation in creatinine due to age, gender, and race.

References

This review by Toffaletti and colleagues gives insights into the issues related to the estimation and measurement of kidney function. It highlights inherent problems not only with serum creatinine measurement and calculation/estimation of GFR (eGFR), but also actual GFR. It also reminds readers that both serum creatinine as well as other markers such as cystatin C are affected by confounders beside variations of GFR. Consequently, the review makes the point that whilst serum creatinine and eGFR derivations may be effective at defining chronic kidney disease stages, they do not accurately reflect measured GFR. The latter is not without its inherent variability and reproducibility. It is important that physicians appreciate these issues when estimating the GFR mainly of those within the ‘normal range’ or those with age-related changes in kidney function.