eGFR: Readjusting Its Rating

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GFR is the accepted metric for evaluating renal function but measuring it directly (mGFR) can be cumbersome, time-consuming, and costly. The constant infusion method using inulin as the filtration marker, introduced in 1934 by Richards and Smith (1), has undergone many revisions that have now made mGFR easier to perform, although not widely available (2,3). A simple, reliable, unbiased, precise, and accurate estimation of mGFR, without reliance on constant infusions or timed urinary collections, would be welcome; however, as illustrated by the extensive compendium of comparisons of mGFR (using classical inulin clearance methods) to eGFR by Botev et al. (4) in this issue of CJASN, this objective is far from being realized.

Although formulaic methods to approximate the values of mGFR from serum creatinine (Scr) levels have been used for many decades, the seminal description of the Modification of Diet in Renal Disease (MDRD) equation (eGFR-MDRD) in 1999 galvanized interest in this common and important clinical issue (5). The often used Cockcroft-Gault equation (6) was never intended to be an approximation of GFR but rather was designed to estimate endogenous creatinine clearance, which is not equivalent to GFR because of the effects of tubular secretion of creatinine (TScr). In normal individuals, this can be compensated for by a correction factor, because TScr is relatively constant (at approximately 22 to 24% of GFR) (7); however, TScr can vary markedly in disease states, particularly those associated with heavy proteinuria (8). Compared with mGFR, the currently widely used eGFR-MDRD formulas (original and reexpressed [5,9]) have limitations because of variable degrees of bias, imprecision, and inaccuracy (10). The studies of Botev et al. (4) in this issue of CJASN provide additional quantitative data on the ranges of bias, precision, and accuracy of eGFR-MDRD according to the levels of mGFR, as measured by inulin clearance. The bias of eGFR declines markedly from −17 ml/min per 1.73 m² when the mGFR is >60 ml/min per 1.73 m² to much lower values when the mGFR is <60 ml/min per 1.73 m². Precision of eGFR is poor at levels of mGFR >60 ml/min per 1.73 m² (1 SD = 21 ml/min per 1.73 m²) but gradually improves (in absolute but not in relative terms) as the mGFR declines. For an mGFR between 30 and 59 ml/min per 1.73 m², the precision of eGFR-MDRD is still poor at 13 ml/min per 1.73 m² (1 SD). Of greater importance is the finding that the accuracy of the eGFR-MDRD actually deteriorates with declining mGFR (p30 = 72% with mGFR >60 ml/min per 1.73 m²; p30 = 63% with mGFR <60 ml/min per 1.73 m²). Thus, eGFR-MDRD has very significant limitations as a method for approximating mGFR, especially when renal function is normal or near normal. It comes as no surprise, therefore, that use of the eGFR-MDRD equation gives rise to many “misclassifications” of chronic kidney disease (CKD) when it is applied to the Kidney Disease Outcomes Quality Initiative (KDOQI)-CKD classification/staging system, which is heavily influenced by eGFR values (11).

One might ask what the use of an estimated, or approximate, GFR value is in clinical practice and whether its inherent imprecision and inaccuracy really matter. The reciprocal relationship of the Scr concentration to mGFR and all of the variables that influence its concentration in serum make it difficult for clinicians to convert a single value in an individual patient to a rough value for GFR by simple mental calculation. Renal function is usually overestimated in this process. Estimating equations remove some of the “guesswork,” and because reductions in GFR are linearly related to loss of renal function on an almost 0 to 100 scale, a low eGFR is more likely to be noticed than a Scr level modestly above the “normal” range for a given laboratory. Sequential changes in the individual patient with unequivocal renal impairment can be very useful in plotting the rate of change and predicting outcomes.

The overriding question is how does the eGFR-MDRD perform in clinical practice? In this respect, the record of eGFR-MDRD is a mixed one (12,13).

For the diagnosis of CKD, as advocated by KDOQI, the eGFR-MDRD is clearly a failure. It frequently leads to errors in assigning individuals to the various categories of CKD. This is due to two complementary characteristics: (1) The intrinsic imprecision and inaccuracy of eGFR compared with mGFR and (2) the use of an absolute threshold for defining stages 3, 4, and 5 CKD rather than a percentile based on age and gender (12). Very clearly, eGFR-MDRD is unsuitable for diagnosing CKD and for the same reason is not suited for screening a general population for CKD (14). Methods for eGFR are also not accurate enough for use in qualifying living donors for renal transplantation (15). An actual mGFR (using 125I-iothalamate, cold iothalamate, iohexol or 51Cr-EDTA, or alternative methods) provides a better assessment of renal function in such individuals.

Conversely, eGFR may be quite useful in determining the
severity of disease in individuals with already well-established kidney disease, provided that they are in a steady state. Indeed, the development of the eGFR-MDRD equation was originally derived from such patients (5). It is now recognized that the variation in Scr concentration as a result of different chemical assays and standards can be overcome by applying a uniform “gold standard” calibration to all clinical laboratories (16). It must also be stressed that malnutrition, obesity, strict vegetarian diets, concomitant drugs, muscle wasting, aging, and underlying disease affect the relationships of Scr-based eGFR to mGFR.

Using eGFR-MDRD as a means of following the progress of established CKD in an individual patient or in a group of patients (as might be exemplified by a clinical interventional trial) may be adequate, but whether it is superior to simple Scr or reciprocal Scr measures is not well established (17). It is not likely that a precise estimate of mGFR is needed in these circumstances.

Much has also been claimed for the value of eGFR as a means for detecting “concealed” renal failure (i.e., a truly abnormal level of mGFR [even after correction for the effects of age and gender]) when the Scr concentration is within the “normal” range for a given laboratory (18)]. Such individuals (often elderly or chronically ill) might also be “at risk” for incorrect dosing of potentially toxic medications, and if they can be identified (accurately) by eGFR, then such adverse events theoretically could be avoided; however, studies comparing the accuracy (by receiver operating characteristic methods) have generally failed to show any advantage of eGFR over simple Scr measurements when gender-specific threshold values or Scr are used (19). More prospective, controlled trials are needed to establish firmly a useful role for eGFR in this area of therapeutics and adverse event avoidance. In this regard, the eGFR-MDRD equation provides values normalized to a body surface area of 1.73 m². This correction can be problematic in very obese or very lean individuals (20).

Finally, eGFR has been used to identify individuals who are at risk for cardiovascular events (21). Although observational studies have demonstrated associations between lower values of eGFR and the increased occurrence of cardiovascular events, a causal relationship is not proved. Indeed, cross-sectional observations from the Prevention of Renal and Vascular Endstage Disease (PREVEND) study suggest that the risk for cardiovascular events is not increased as eGFR declines from stage 1 to stage 3 CKD, unless abnormal albuminuria is concomitantly present (22). The use of eGFR alone as a means of stratifying patients who are at risk for fatal or nonfatal cardiovascular events does not seem to be appropriate at this time.

The substantial efforts of Botev et al. (4) to characterize the bias, precision, and accuracy of methods for estimating mGFR (by inulin clearance) has its inherent weaknesses in design, but the message is clear: If the objective is to provide a reasonably exact value for mGFR, then current formulaic approaches based on Scr have fallen short. A search for new methods, rather than modifications of the current approach, seems to be in order. Reliable and simple biomarkers of functional disturbances of the kidney accurately reflecting disease are needed for both diagnosis and monitoring of interventions. Quantification of albuminuria is one such promising avenue, but others are in the development stage (23).

The “eGFR concept” is becoming ever more firmly embedded in clinical medicine even as its deficiencies are increasingly recognized. New, more accurate, and universally applicable methods for evaluating renal function will likely be slow to emerge. In the interim, it seems to us that several recommendations are in order: (1) Clinicians (including non-nephrologists) must be educated regarding the errors that are inherent in formulaic approaches to eGFR; (2) eGFR should not be used for diagnosis of or screening for CKD unless the definitions are changed and normal ranges are better defined; however, eGFR could be used for monitoring the progression of an already established CKD; (3) measurement of GFR by accurate methods (e.g., by radioactive or cold iothalamate or iohexol) should be encouraged whenever a precise value for GFR is truly needed; (4) universal standardization of Scr measurements against a gold standard should continue to be pursued in all laboratories (hospital and outpatient); and (5) routine (mandatory) reporting of eGFR whenever a Scr is measured in a hospital or an outpatient laboratory should be abandoned as a matter of public and professional policy.

Disclosures
None.

References