Mini-Review

Methods of Estimating GFR – Different Equations Including CKD-EPI

[*]Christopher M Florkowski,[1] Janice SC Chew-Harris[2]
[1]Clinical Biochemistry Unit, Canterbury Health Laboratories, Christchurch 8011, [2]Department of Biochemistry, Medlab South Ltd, Christchurch 8013, New Zealand.
[*]For correspondence: Dr Christopher Florkowski, Chris.Florkowski@cdhb.govt.nz

Abstract
The initiative for estimating glomerular filtration rate (GFR) derives from the limitations of interpreting plasma creatinine alone, the cost and complexities of determining a gold standard GFR with either inulin or radionuclides, and the inaccuracies inherent in measuring a 24 h urine creatinine clearance. In August 2005, the Australasian Creatinine Consensus Working Group recommended that an eGFR based on the abbreviated MDRD (Modification of Diet in Renal Disease) formula shall be automatically calculated for every request for creatinine in people over 18 years. Uptake was almost universal, though with appropriate caveats in place regarding potential limitations. Updated recommendations in 2007 recognised uniform standardisation of the plasma creatinine assay. A recent development is the CKD-Epidemiology Collaboration (CKD-EPI) equation which confers less underestimation of GFR in subjects with normal renal function. Cystatin C and its derivative equations may have advantages in some situations.

Serum Creatinine as an Index of Kidney Function and its Inherent Limitation

Traditionally, a single measure of plasma creatinine has been used to determine glomerular function and by corollary, diagnosis and staging of chronic kidney disease (CKD). For any individual, plasma creatinine values are tightly distributed around a homeostatic set-point, with an intra-individual variation (CVi) of 5.3%.[1] The consequence of this is that an individual may show a significant increase in plasma creatinine with deterioration in renal function, yet still have a result which falls within the reference interval. Furthermore, plasma concentrations of creatinine are affected by other factors including muscle mass, diet, gender, age and ethnicity. A very lean elderly woman with renal impairment, for example, may have a 'normal' plasma creatinine despite a reduced GFR. Conversely a very muscular subject may have an apparently 'abnormal' creatinine despite having a normal GFR. These limitations have focused attention on more direct measurement of GFR.

GFR and Creatinine Clearance

The perfect filtration marker: is not protein bound, is freely filtered by the glomerulus, is without any tubular secretion, is not metabolised by the kidneys, and is physiologically inert. Very few substances fulfil these criteria: the gold standard has been a plant polysaccharide called inulin, an exogenous substance requiring injection and a complex collection protocol; alternatives involve administration of radionuclides such as ^{125}I-iothalamate, ^{51}Cr-EDTA or ^{99m}Tc-DTPA, which are labour-intensive procedures and too costly for routine use. None of these techniques is suitable as a screening procedure for the detection of CKD.

In the past, a 24 h urine creatinine clearance has been regarded as a more sensitive tool for the detection of kidney failure than a single plasma creatinine measurement. However, the inconvenience of a timed urine collection, failure to collect the entire specimen, and the wide (11%) within-subject variability, restrict the usefulness of this procedure. Furthermore, there is some tubular secretion of creatinine and as a result, healthy individuals could have a creatinine clearance regularly exceeding that of inulin clearance by 10 to 40%, thereby overestimating GFR and masking any future renal impairment.[2]

Introduction of eGFR

While recognising the inadequacies of plasma creatinine and a 24 h creatinine clearance, the National Kidney Foundation Disease Outcomes Quality Initiative (K-DOQI) recommended use of estimates of GFR calculated from prediction equations based on plasma or serum creatinine.[3]

In 1976, Cockcroft and Gault published an equation to predict creatinine clearance based on age, weight, height and

plasma creatinine, together with correction factors.[4] Although helpful, it has many inherent limitations, having been derived mostly from hospitalised men (with only nine females in the cohort), all of whom had CKD. The requirement for weight and height to be provided also restricted its ability to be reported by the laboratory. Despite these shortcomings, it has achieved a considerable prominence, more through cumulated experience than a solid evidence base. It is remarkable that for guiding the administration of many drugs, the FDA (US Food and Drug Administration) and other bodies still stipulate that creatinine clearance should be estimated by the Cockcroft-Gault equation.

The MDRD study was based on a multicentre trial to evaluate the effect of dietary protein restriction and blood pressure control on progression of renal disease in 1628 patients with CKD, with the added objective of developing an equation that could improve the prediction of GFR from plasma creatinine.[5] GFR was measured as the renal clearance of ^{125}I-iothalamate, and creatinine clearance was computed from creatinine excretion in a 24 h urine collection and a single measurement of plasma creatinine. Stepwise multiple logistic regression analysis was employed to determine the set of variables that best predicted GFR.[5] A 6-variable equation was derived, and subsequently a simplified 4-variable version which included age, gender, plasma creatinine value and race differentiation as white or black was published (equation 1, Table). Results were expressed as per 1.73 m^2 of body surface area.[5]

The advantage of this equation over Cockcroft and Gault's was the lack of requirement for either body weight or height to be supplied and it became the preferred equation. The MDRD study equation was subsequently validated in patients with diabetic kidney disease, renal transplant recipients, and African-Americans with non-diabetic kidney disease. Given that the MDRD equation was originally derived from a group of CKD patients, its utility for healthy individuals remains unclear, and strictly it has not been validated in children under 18 years of age, in pregnant women, in patients above 70 years of age, and in ethnic groups other than African-American. More importantly, given the rise in the epidemic proportions of global obesity, the MDRD equation has not yet been validated at extremes of body weight, further limiting its usefulness in targeting individuals at higher risks of developing CKD.

Poorer performance of the MDRD formula is reported at low plasma creatinine concentrations.[6] Calibration bias and measurement imprecision for plasma creatinine have a large impact on the uncertainty in eGFR, especially with lower plasma creatinine values (corresponding to higher levels of renal function).[7] It was recognised that there was a positive systematic bias for plasma creatinine concentrations analysed with the Beckman Coulter CX3 in the original MDRD study. To overcome the error from instrument bias, a unified effort to standardise creatinine measurements to the reference isotope-dilution mass spectrometry (IDMS) method was encouraged

Table. eGFR prediction equations based on plasma creatinine concentration.

MDRD eGFR = 186 x [Plasma Creatinine (µmol/L) x 0.0011312] $^{-1.154}$
x [age (years)] $^{-0.203}$
x [0.742 if female] x [1.212 if black] [equation 1]

MDRD eGFR (IDMS aligned) = 175 x [Plasma Creatinine (µmol/L) x 0.0011312] $^{-1.154}$
x [age (years)] $^{-0.203}$
x [0.742 if female] x [1.212 if black] [equation 2]

CKD-EPI eGFR;

Female with Creatinine < 62 µmol/L; use eGFR = 144 x $(Cr/61.6)^{-0.329}$ x $(0.993)^{Age}$
Female with Creatinine > 62 µmol/L; use eGFR = 144 x $(Cr/61.6)^{-1.209}$ x $(0.993)^{Age}$
Male with Creatinine < 80 µmol/L; use eGFR = 141 x $(Cr/79.2)^{-0.411}$ x $(0.993)^{Age}$
Male with Creatinine > 80 µmol/L; use eGFR = 141 x $(Cr/79.2)^{-1.209}$ x $(0.993)^{Age}$

[equation(s) 3]

where Cr is the plasma creatinine (µmol/L)

in laboratories around the world. With this, a new factor of '175' (as opposed to '186') was subsequently recommended in the MDRD equation for creatinine assays that are IDMS-aligned (equation 2, Table).[8]

Comparative performance of the MDRD and the Cockcroft-Gault formulae has been assessed in numerous studies. Generally, the MDRD has been shown to perform somewhat better than Cockcroft-Gault in a majority of the studies, with less bias and a higher proportion of results in agreement with a radionuclide gold standard.[9,10] However the Cockcroft-Gault formula has been reported to be more accurate when plasma creatinine is within the reference interval.[11] Recalibration of creatinine assays to align with IDMS has been shown to improve the performance of the MDRD equation.[12]

Australasian Recommendation of eGFR Reporting

In August 2005, the Australasian Creatinine Consensus Working Group recommended that an eGFR based on the abbreviated MDRD formula be automatically calculated for every request for plasma creatinine in people over 18 years.[13] Updated recommendations in 2007 further addressed some of the more contentious areas and also recognised IDMS-aligned standardisation of the plasma creatinine assay, emphasising adoption of the '175' as opposed to '186' version of the MDRD equation.[14]

The original recommendations stipulated that eGFR be reported in mL/min or mL/min/1.73m^2.[13] Moreover, an eGFR was to be reported for all patients above 18 years of age, and all values greater than 60 mL/min/1.73m^2 were to be reported as '>60 mL/min/1.73m^2' rather than an exact figure. In the 2007 revised recommendations, the limit for reporting an exact figure was raised to >90 mL/min/1.73m^2.[14]

Although GFR is recognised to decline with age, it is debated whether this is a truly physiological or pathological change. Age-adjusted reference intervals have not been recommended as it has been argued that it is difficult to accommodate the opposing effects of rising creatinine due to reduced renal function and declining creatinine due to reduced lean body mass. The revised recommendations also advised caution in interpretation of eGFR values in the range of 45-59 mL/min/1.73m^2 in people over 70 years old.[14]

A dosage reduction is often necessary for renally excreted drugs to avoid toxic effects (see Doogue, page 69 in this issue). Revised recommendations allow the use of eGFR (by MDRD) when no other measure of true GFR is possible, but in practice the Cockcroft-Gault equation is still more widely used by clinicians. For critically important drugs, for example cis-platinum in chemotherapy, the recommendations advocate more formal assessment of GFR.

Despite suggesting a correction factor for African-Americans with the original MDRD study, there is limited data on the use of eGFR in other ethnic groups. The Australasian recommendations stated that for Australian Aborigines and Torres Strait Islanders and New Zealand Māori, eGFR should continue to be reported with every creatinine request while recognising the need for more studies to be undertaken.[14] Notwithstanding the difficulty of assigning ethnicity in any individual, one of the main confounding variables is most likely to be lean body mass, rather than BMI *per se*. At higher levels of BMI, evidence shows Polynesians to be significantly leaner than their European counterparts, suggesting a body composition with higher muscle mass.[15] Further studies are ongoing in Australian Aborigines, including detailed assessments of body composition with DEXA scans and bioelectrical impedance measurements.

While the foregoing variables merit consideration, achieving a steady state for plasma creatinine is the single most important factor for interpretation of eGFR and yet frequently it is not fulfilled, especially in acutely unwell patients. Of course, such a condition applies equally to interpretation of plasma creatinine alone.

CKD-EPI Equation

Given that the MDRD equation was developed in a population with sub-optimal kidney function, its accuracy in predicting GFR is best reflected in those with mild kidney impairment. It is recognised that MDRD tends to underestimate renal function in those with a normal eGFR >90 mL/min/1.73m^2. In response to these concerns, the CKD-Epidemiology Collaboration group (CKD-EPI) developed and validated a new equation in 2009 designed to match the accuracy of the MDRD equation at GFR <60 mL/min/1.73m^2 and to offer greater accuracy at higher GFR, minimising the over-diagnosis of CKD with the MDRD equation.[16] The new CKD-EPI equation was developed from 8254 data points from six studies and four clinical populations, with original serum creatinine values recalibrated to the Roche enzymatic method.[16] The CKD-EPI equation (equation 3, Table) includes log serum creatinine (modelled as a 2-slope linear spline with sex specific knots at 62 µmol/L in women and 80 µmol/L in men), with gender, race and age on the natural scale. It is therefore effectively four different equations for whites (men, women, above the knot value, below the knot value) and another four for African-Americans in whom a different factor is used. The CKD-EPI equation was shown to be as accurate as MDRD in the subgroup with eGFR <60 ml/min/1.73m^2 and substantially

more accurate in the subgroup with eGFR >60 ml/min/ 1.73m^2.

Improved accuracy of the CKD-EPI equation could have important implications for public health as well as in clinical practice. Application of the CKD-EPI equation in the Australian, Diabetes, Obesity and Lifestyle (AusDiab) Study yielded a lower estimated prevalence of CKD compared with the MDRD equation, namely 11.5% (95% CI: 9.4-14.1) compared with 13.4% (95% CI: 11.1-16.1).[17] The reclassification of individuals as normal appeared appropriate in that this group had lower cardiovascular risk.[17] Extrapolated to whole populations, it means that fewer individuals will be assigned as having CKD and thus resources can be more appropriately targeted.

Cystatin C as a Marker of Kidney Function

Many studies have compared cystatin C concentrations or cystatin C-derived equations with gold standard methods. Most studies have found cystatin C or the reciprocal of cystatin C to be superior, or at least equivalent to serum creatinine for the detection of decreased GFR. Two meta-analyses concluded cystatin C to be superior to creatinine in predicting renal function.[18,19] Several equations based on cystatin C have also been published.[20] Two types of cystatin C method are currently available commercially, i.e. nephelometry and turbidimetry, with nephelometry reported to be the more accurate.[21] The lack of an international standardised calibrator currently limits the use of cystatin C equations. More importantly and to justify its additional cost, its use will depend on evidence that it significantly improves clinical outcomes.

Future of eGFR Equations

In the immediate future, the CKD-EPI equation will probably emerge as the equation of choice to estimate GFR. Cystatin C and its derivative equations offer some advantages over plasma creatinine, but the extra cost will not justify its use until there is compelling evidence suggesting improved clinical decision making and better outcomes.

In the final analysis, we need to remember that all equations for GFR estimation are essentially mathematical abstractions that relate patients to the populations from which the equations were derived. Inevitably, therefore, there is no ideal "one size fits all" equation, and clinicians need to be mindful of all the potential limitations in their application and to interpret results in a full clinical context.

Competing Interests: None declared.

References

1. Biological variation database specifications. http://www.westgard.com/biodatabase1.htm (Accessed 15 November 2010).
2. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992;38:1933-53.
3. National Kidney Foundation Guidelines. http://www.kidney.org/professionals/kdoqi/guidelines.cfm (Accessed 15 November 2010).
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16: 31-41.
5. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
6. Lin J, Knight EL, Hogan ML, Singh AK. A comparison of prediction equations for estimating glomerular filtration rate in adults without kidney disease. J Am Soc Nephrol 2003;14:2573-80.
7. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 2006;52:5-18.
8. Levey AS, Coresh J, Greene T, Stevens LA, Zhang Y, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247-54.
9. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P. Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. J Am Soc Nephrol 2005; 16:763-73.
10. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005;16:459-66.
11. Bostom AG, Kronenberg F, Ritz E. Predictive performance of renal function equations for patients with chronic kidney disease and normal serum creatinine Levels. J Am Soc Nephrol 2002;13:2140-4.
12. Stevens LA, Manzi J, Levey AS, Chen J, Deysher AE, Greene T, et al. Impact of creatinine calibration on performance of GFR estimating equations in a pooled individual patient database. Am J Kidney Dis 2007;50:21-35.
13. Mathew TH; Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: A position statement. Med J Aust 2005;183:138-41.
14. Mathew TH, Johnson DW, Jones GR; Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular

filtration rate: revised recommendations. Med J Aust 2007;187:459-63.
15. Swinburn BA, Ley SJ, Carmichael HE, Plank LD. Body Size and composition in Polynesians. Int J Obes Relat Metab Disord 1999;23:178-83.
16. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
17. White SL, Polkinghorne KR, Atkins RC, Chadban SJ. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) Study GFR estimating equations; The AusDiab (Australian Diabetes, Obesity and Lifestyle) Study. Am J Kidney Dis 2010;55:660-70.
18. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002;40:221-6.
19. Roos JF, Doust J, Tett SE, Kilpatrick CM. Diagnostic accuracy of cystatin C compared to serum creatinine for the estimation of renal dysfunction in adults and children – a meta-analysis. Clin Biochem 2007;40: 383-91.
20. Chew JS, Saleem M, Florkowski CM, George PM. Cystatin C – A paradigm of evidence based laboratory medicine. Clin Biochem Rev 2008;29:47-62.
21. Mussap M, Plebani M. Biochemistry and clinical role of human cystatin C. Crit Rev Clin Lab Sci 2004;41:467-550.