Sultan Qaboos University Med J, May 2014, Vol. 14, Iss. 2, pp. e152-154, Epub. 7th Apr 14
Submitted 20th Nov 13
Revision Req. 13th Feb 14; Revision Recd. 14th Feb 14
Accepted 16th Feb 14

EDITORIAL

Advances in Glomerular Filtration Rate Estimation

Malik A. Rabbani

تطورات في تقدير سرعة الترشيح الكبيبي

أنس مالك الرباني

Renal function is an indication of the state of the kidney and its role in renal physiology. Various conditions, diseases and drugs can affect the function of the kidneys. In clinical practice, plasma concentrations of the waste substances of creatinine and urea as well as electrolytes are used by physicians to determine renal function. Although these measures are adequate to determine whether a patient is suffering from kidney disease, blood urea nitrogen (BUN) and creatinine will not be raised above the normal range until 50% of total kidney function is lost.[1] Hence, whenever renal disease is suspected or careful dosing of nephrotoxic drugs is required, the more accurate glomerular filtration rate (GFR), or its approximation by the creatinine clearance, is measured. The estimated glomerular filtration rate (eGFR) does not diagnose any kidney disease but is a test to assess how well your kidneys are working. During last few decades, various equations have evolved in an attempt to precisely measure GFR. Given SQUMJ articles on GFR in this and the previous issue, this editorial will discuss the latest advances made in GFR estimation.[2–4]

The level of GFR is accepted as the most useful index of kidney function in both healthy and diseased states. The determination of the GFR is a cumbersome procedure, ideally involving inulin infusion and urine collection under very standardised conditions. GFR is also estimated by measuring the clearance of other exogenous filtration markers such as iothalamate, iohexol and ^{51}chromium ethylene-diamine-tetra-acetic acid [^{51}Cr] EDTA or technetium-^{99m}-diethylenetriaminepentacetic acid [^{99m}Tc] DPTA. However, these methods are expensive and require exposure to radiation and compliance with strict regulatory guidelines, and thus have limited use in the routine laboratory settings. Besides, these tests are performed only when accurate information on kidney function is mandatory.

Serum creatinine (Cr), on the other hand, is freely filtered and has minimal tubular secretion and absorption. Its estimation from random blood samples is simple and inexpensive. It has relatively good accuracy and, for precisely these reasons, it has become a valuable clinical tool for estimating GFR. In clinical practice, a rise in serum Cr is used as a marker of reduced GFR, indicating it is inversely related with GFR. GFR can be estimated by measuring Cr clearance using serum Cr levels and a timed urine specimen.

There are, however, limitations on the use of serum Cr as an indirect filtration marker because of its biological variability, bias and non-specificity which affect Cr measurement, medication effects, nutrition and the alterations in circulating serum Cr produced by non-renal disease states.

Because of the differences in GFR range and Cr production between the two populations—healthy people *versus* patients with chronic kidney disease (CKD)—the estimation of GFR by serum Cr also differs between healthy people and patients with CKD. Hence, there is a risk of overestimating the GFR as a result of these confounding factors; in addition, we know that the magnitude of the overestimation is not predictable.[5] This proportional variation in the GFR is larger in populations with the disease than in populations without it. As a result, a larger proportion of the variation in serum Cr levels among patients with the disease is due to a variation in the GFR, not to a variation in the other determinants as compared with healthy people. For example, among patients with the disease, a difference in levels of serum Cr of 0.8 and 1.2 mg per decilitre (70.7 and 106.1 μmol per litre) probably reflects a difference in the GFR. In contrast, this same difference among healthy people more likely reflects a difference in muscle mass or protein intake rather than the GFR. When an estimating equation

Queen's Hospital, Burton Hospitals NHS Foundation Trust, Burton upon Trent, Staffordshire, UK
E-mail: anasrabbani@yahoo.com

derived in a population with CKD is applied to a healthy population, the equation will overstate the strength of the relationship of the GFR with the level of serum Cr. Thus, in people with an unusually low or high estimated GFR, the measured GFR would tend to fall closer to the normal GFR of the population than the GFR estimates.

Despite these limitations, plasma Cr is still measured as an estimate of the GFR in clinical practice, on the assumption that Cr is completely filtered across the glomerulus and that Cr production and excretion are constant. The limitations of Cr clearance and inulin clearance have inspired researchers to seek out easy formulas to estimate GFR.

The Cockcroft and Gault (C&G) formula is employed to measure Cr clearance, using plasma Cr concentration with a correction for age, sex and muscle mass.[6] The C&G formula is effective only when plasma Cr is in a steady state; it is also inaccurate in cases of liver disease, oedema and muscle wasting or extreme adiposity.

It is important to remember that GFR estimation equations are mainly used for the systematic staging of CKD and should not be used in the setting of an acute rise in serum Cr. The modification of diet in renal disease (MDRD) GFR equation is mostly used for the estimation of GFR. It often out-performs the C&G equation in populations with a low range of GFR.[3] However, even this equation has several limitations, including age, disease state, and considerable variations in the standardisation of the serum Cr assays.

Plasma cystatin C (cys C) was proposed some years ago as an alternative endogenous substance for serum Cr in estimating the GFR because it has many properties of an ideal marker for GFR.[7] Cys C is claimed to be a promising marker to monitor glomerular dysfunction, having a higher sensitivity and specificity than serum Cr and Cr clearance for small changes in GFR.[4] Because of availability of immunonephelometric[8] and immunoturbidimetric[9] methods, which allow a rapid and precise routine measurement, cys C has become a subject of great interest. A number of studies comparing cys C with plasma Cr have proved cystatin C is a more sensitive indicator of mild reductions of renal function than plasma Cr.[10] However, despite considerable evidence, its role as an alternate marker for estimating GFR is still limited in clinical practice. There are several reasons for this, for example, a general diffidence among clinicians, the absence of definitive cut-off values, conflicting results in clinical studies, no clear evidence on when and how to request the test, the poor commutability of results and no accurate examination of costs and of its routine use.

Despite these facts, there are certain cases where Cr measurement is not appropriate; for example, cys C may be more reliable in cases with liver cirrhosis, beta thalassemia,[4] morbid obesity and malnourished patients with a reduced muscle mass. This is true as we know that cys C is produced at a constant rate in all body cells, excreted by glomerular filtration and followed by catabolism in the tubular cells. Besides, it is also now known that there are non-GFR determinants of its serum level[11,12] and there are studies suggesting that cys C is less dependent upon muscle mass than Cr, and therefore should provide more accurate estimate of GFR particularly in populations with differences in muscle mass.[4,9–12]

The more recent Cr-based formula, the Mayo Clinic Quadratic (MCQ) equation[13] and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation proposed in 2009[14] improve underestimation, a well-recognised fact seen with the MDRD formula in patients with preserved kidney function, as both MCQ and CKD-EPI were derived from populations that included subjects with normal renal function.

The CKD-EPI equation was developed in a pooled dataset from 10 studies that included participants of diverse clinical characteristics, with and without kidney disease, and validated in a separate dataset pooled from 16 additional studies.[13] The CKD-EPI equation was found to be more accurate than the MDRD Study equation, in the 16 studies used for its validation, with lower bias especially at an estimated GFR greater than 60 ml/min per 1.73 m^2; however, the precision was not substantially improved compared to the MDRD Study equation.[14] Besides, there are weaknesses to this study, including relatively few participants older than 70 years of age and racial minorities other than black, incomplete data on diabetes type, immunosuppressive agents for transplantation, measures of muscle mass and other clinical conditions and medications that might affect serum Cr independently from GFR. In addition, the CKD-EPI equation does not overcome the limitations of serum Cr as an endogenous filtration marker. Moreover, a comparison between MDRD and MCQ equations for GFR estimates provides significantly different results as the MCQ estimate provides suspiciously high GFR values. However, only direct comparison using the costly and complex clearance of an exogenous marker could unequivocally confirm the superiority of one method over the other.

Despite these limitations, serum Cr remains central at the present time for the evaluation of kidney function in clinical practice, and GFR estimates based on serum Cr will continue to be used in clinical practice for the foreseeable future.

Further research is necessary to improve GFR estimation. Non-GFR determinants of Cr seem to be responsible for imprecision in GFR estimation. Measurement error in GFR also seems to contribute to this imprecision. Research, therefore, should be directed not only towards improving GFR measurement but evaluating the novel filtration markers for GFR estimation, either alone or in combination with serum Cr.[15] Moreover, studies in representative populations, especially the elderly and racial and ethnic minorities, are also necessary.

In conclusion, significant advances have been made which have revolutionised our understanding of the performance and utilisation of GFR estimation in the current era. It is quite evident that a single equation will unlikely work equally well in all populations. However, given the current understanding, we believe, despite its limitations, that the new CKD-EPI equation, which uses the same four variables as the MDRD Study equation developed in people with and without kidney disease, has improved bias and risk prediction, without compromising the accuracy in people with CKD. It is an important step forward and should replace the MDRD Study equation for routine clinical use.

References

1. Paige NM, Nagami GT. The top 10 things nephrologists wish every primary care physician knew. Mayo Clin Proc 2009; 84:180–6. doi: 10.1016/S0025-6196(11)60826-4.
2. Al-Maqbali SRS, Mula-Abed W-AS. Comparison between three different equations for the estimation of glomerular filtration rate in Omani patients with type 2 diabetes mellitus. Sultan Qaboos Univ Med J 2014; 14:184–90.
3. Al-Osali ME, Al-Qassabi SS, Al-Harthi SM. Assessment of glomerular filtration rates by Cockcroft-Gault and modification of diet in renal disease equations in a cohort of Omani patients. Sultan Qaboos Univ Med J 2014; 14:70–7.
4. Ali BA, Mahmoud AM. Frequency of glomerular dysfunction in children with beta thalassaemia major. Sultan Qaboos Univ Med J 2014; 14:86–92.
5. 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.
6. Jones GR, Imam S. Validation of the revised MDRD formula and the original Cockcroft and Gault formula for estimation of the glomerular filtration rate using Australian data. Pathology 2009; 41:379–82. doi: 10.1080/00313020902884980.
7. Zhang Z, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analy. Am J Kidney Dis 2011; 58:356–65. doi: 10.1053/j.ajkd.2011.02.389.
8. Whicher JT, Price CP, Spencer K. Immunonephelometric and immunoturbidimetric assays for proteins. Crit Rev Clin Lab Sci 1983; 18:213–60.
9. Schwartz GJ, Schneider MF, Maier PS, Moxey-Mims M, Dharnidharka VR, Warady BA, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int 2012; 82:445–53.
10. Madero M, Sarnak MJ, Stevens LA. Serum cystatin C as a marker of Glomerular filtration rate. Curr Opin Nephrol Hypertens 2006; 15:610–6.
11. Stevens LA, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int 2009; 75:652–60. doi: 10.1038/ki.2008.638.
12. Grubb A, Bjork J, Lindstrom V, Sterner G, Bondesson P, Nyman U. A cystatin C-based formula without anthropometric variables estimates glomerular filtration rate better than creatinine clearance using the Cockcroft-Gault formula. Scand J Clin Lab Invest 2005; 65:153–62.
13. Fontseré N, Bonal J, Salinas I, de Arellano MR, Rios J, Torres F, et al. Is the new Mayo Clinic Quadratic equation useful for the estimation of glomerular filtration rate in type 2 diabetic patients? Diabetes Care 2008; 31:2265–7. doi: 10.2337/dc08-0958.
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150:604–12.
15. Lee D, Levin A, Roger SD, McMahon LP. Longitudinal analysis of performance of estimated glomerular filtration rate as renal function declines in chronic kidney disease. Nephrol Dial Transplant 2009; 24:109–16. doi: 10.1093/ndt/gfn477.