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Review Article

Estimated Glomerular Filtration Rate (eGFR): A Serum Creatinine-Based Test for the Detection of Chronic Kidney Disease and its Impact on Clinical Practice

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Abstract

Chronic kidney disease (CKD) is an important epidemic and public health problem that is associated with a significant risk for vascular disease and early cardiovascular mortality as well as progression of kidney disease. Currently it is classified into five stages based on the glomerular filtration rate (GFR) as recommended by many professional guidelines. Radiolabelled methods for measuring GFR are accurate but not practical and can be used only on a very limited scale while the traditional methods require timed urine collection with its drawback of inaccuracy, cumbersomeness and inconvenience for the patients. However, the development of formula- based calculation of estimated GFR (eGFR) has offered a very practical and easy approach for converting serum creatinine value into GFR result taking into consideration patient's age, sex, ethnicity and weight (depending on equation type). The commonly used equations include Cockraft and Gault (1976), Modification of Diet in Renal Disease (MDRD) (1999) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (2009). It is the implementation of these equations particularly the MDRD that has raised the medical awareness in the diagnosis and management of CKD and its adoption by many guidelines in North America and Europe. The impact and pitfalls of each of these equations in the screening, diagnosis and management of patients with CKD are presented and discussed in this review.

Keywords: eGFR; Chronic kidney disease; Cockraft and Gault; MDRD; CKD-EPI.

Introduction

Assessment of renal function represents the commonest core laboratory testing that is performed worldwide. The increasing prevalence of many chronic diseases particularly diabetes mellitus, hypertension, cardiovascular and renal diseases together with the increasing medical care and its impact on improving life expectancy have all centered on the importance of organs functions assessment including most importantly renal function. Chronic kidney disease (CKD) is also a significant risk factor for vascular disease and early cardiovascular mortality as well as progression of kidney disease.[1]

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Classification and Diagnosis of Chronic Kidney Disease

CKD is classified based on glomerular filtration rate (GFR), as recommended by the US- based National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI), and adopted by the Kidney Disease Improving Global Outcomes (KDIGO) as well as the National Service Framework (NSF) for Renal Services and Kidney Disease and National Institute of Health and Clinical Excellence (NICE).[2] This classification provides the basis for the management of CKD. Accordingly, CKD is classified into five stages: stage 1 (kidney damage with normal or increased GFR ≥90), stage 2 (kidney damage with mildly decreased GFR 60-89), stage 3 (moderately decreased GFR 30-59), stage 4 (severely decreased GFR 15-29), and stage 5 (kidney failure, GFR <15) [all GFR in mL/min/1.73 m^2]. For the diagnosis of stage 1 and stage 2 CKD, an evidence of kidney damage for ≥3 months is required as manifested by pathological kidney abnormalities or abnormal urine composition (such as haematuria or proteinuria), or abnormalities in imaging tests. Recent guidance from NICE has recommended sub-classifying CKD stage 3 into 3A (GFR 45-59 mL/min/1.73 m^2) and stage 3B (GFR 30-44 mL/min/1.73 m^2), each with different level of risk. NICE guidance also recommended the use of suffix (p) to denote the presence of proteinuria when staging CKD, using random urine albumin-to-creatinine ratio in preference to protein-to-creatinine ratio.[3] In the NSF for Renal Services, the term 'kidney failure' in the NKF classification is replaced by 'established renal failure' (ERF) defined as CKD which has progressed so that renal replacement therapy (RRT) is needed to maintain life.[2]

The prevalence of CKD is so high that is simulates a worldwide epidemic and public health problem all over the world. In UK, the prevalence of CKD stage 3-5 (GFR <60 mL/min/1.73m^2) is estimated to be 8.5%,[4] and based on a review of 26 studies a prevalence of CKD of 7.2% in patients aged >30 years and a prevalence of 23.4-35.8% in patients aged >64 years were reported.[5] In US, the prevalence of CKD based on data from the Third National Health and Nutrition Examination Survey (NHANES III) was 11% (3.3% with stage 1; 3.0% with stage 2; 4.3% with stage 3; 0.2% with stage 4; and 0.2% with stage 5).[6] Also, the United States Renal Data System (USRDS), a national database for CKD patients receiving RRT, reported an estimate prevalence of end-stage renal disease (ESRD) in US population of 344,000, with only small proportion of CKD patients are on RRT which represents the tip of a large iceberg.[7] There has been a growing awareness about CKD for the last decade in parallel with publication of the CKD stages classification by NKF-K/DOQI in 2002 which was adopted by the other guidelines.[2] Early detection and treatment of kidney disease/damage should be aimed to slow or prevent any progression in kidney dysfunction, and hence to prevent or delay the need for RRT and reduce the associated risk of cardiovascular death. Screening populations at risk of developing CKD is considered now to be a major challenge in the management of patients with underlying chronic diseases and is of much interest particularly to Clinicians including Nephrologists, Diabetologists, and General Practitioners.

Formula- Based Calculation of eGFR

The approach of screening for any underling kidney damage has been facilitated and become routinely available with the advent of calculating the estimated GFR (eGFR) from serum creatinine based on formulae that take into consideration a number of patient's characteristics. By this approach, the result of serum creatinine is converted into physiological units of GFR. The creatinine- based calculated eGFR has improved the validity of serum creatinine which is considered alone an insensitive index of glomerular function whereby at least approximately 50% of glomerular function has to be lost before creatinine is raised in the blood.[8] It is also influenced by muscle mass, age, gender and race. Despite the ongoing analytical improvement in the techniques of creatinine measurement, however still it is suffering from limited sensitivity and specificity, analytical interferences and standardization problems.[9] Serum creatinine is a poor screening test for CKD in elderly patients especially women and may fail to identify 50% of patients with CKD stage 3.[10] On the other hand, measurement of GFR using exogenous (radiolabeled or non-radiolabeled) such as ^{51}Cr labeled Ethylenediaminetetraacetic acid (EDTA), ^{99m}Tc labeled Diethylenetriaminepentaacetic acid (DTPA), ^{125}I-Iothalamate, Iohexol, inulin, or endogenous approaches such as creatinine clearance appear to be more accurate but cumbersome, labour intensive, costly and impractical for wide application.[8] The most commonly used 24 hr creatinine clearance suffers from the disadvantage of the need for 24 hr urine collection with its known drawbacks of wide intra-individual variation, inaccuracy and inconvenience when collecting timed urine specimens.[8]

Development of formula- based calculation of eGFR has offered approaches for converting serum creatinine value (with its limitations when reported alone) into GFR result (with its advantage in reflecting glomerular function status). Until 1999, there were more than 25 of such formulae with Cockraft and Gault formula[11] appears to be the most attractive and validated one in adults where by:

$$\text{eGFR (mL/min)} = [(140 - \text{age}) \times \text{Wt} / (0.814 \times \text{S.Cr in } \mu\text{mol/L})] \times (0.85 \text{ if female})$$

[eGFR has to be corrected for surface area]

This equation gained application for its better correlation (r=0.83) when evaluated against ^{125}Iothalamate GFR compared with 24 hr creatinine clearance (r= 0.69).[12] However, the need for body weight in the equation has greatly limited its practicability for wide use in renal medicine. In 1999, a great change in the utilization of creatinine- based calculation of GFR was launched in practice by Levey *et al*[13] who validated a new equation for calculating eGFR based on serum creatinine, age, sex and ethnicity as well as urea and albumin using 6- variables Modification of Diet in Renal Disease (6-v MDRD) equation. The inclusion of urea and albumin was a limitation for the added cost and analytical variation. Recognizing this, in 2000 Levey *et al*[14] subsequently published a 4-variables (4-v MDRD) equation that does not require albumin and urea with no impact on accuracy, whereby:

$$\text{eGFR (mL/min/1.73m}^2) = 186\ (\text{S.Cr in } \mu\text{mol/l} \times 0.011312)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African/American Black})$$

The constant factor of 186 stated in the original equation was then recommended by the same authors to be re-expressed using a constant of 175, if creatinine measurement is standardized against Isotope Dilution-Mass Spectrometry (ID-MS) reference method.[15]

It is the simplicity and practicability of this MDRD equation which does not require body weight, report GFR in mL/min/1.73 m^2 without need for correction of surface area, and which was validated against ^{125}Iothalamate GFR in large population across a wide range of GFR, that ease its wide application in laboratory practice. From then, eGFR derived from serum creatinine based MDRD equation gained worldwide spread in reporting renal function test. This approach started to gain a core role as a suitable measure of kidney function that was quickly understood by almost all physicians. It is this development in eGFR reporting from serum creatinine that drive the international professional societies such as NKF-K/DOQI, KDIGO, NICE and NSF for Renal Services and Kidney Disease, towards implementing eGFR in the classification and management of CKD. Thereafter, in UK from April 2006 it was decided by the Department of Health (DH) based on recommendation from the NSF for Renal Services and Kidney Disease to report MDRD formula-based eGFR for kidney function testing when serum creatinine is measured in all National Health Service (NHS) Laboratories. This was recommended in order to prevent people developing kidney disease in the first instance or to slow down the progression of kidney damage and minimize cardiovascular risk when a diagnosis has been made.[16] Accordingly, the DH recommended that the Local Health Organisations have to work with Pathology Services and Networks to develop protocols for measuring kidney function by serum creatinine concentration together with a formula-based estimation of GFR, calculated and reported automatically by all Clinical Biochemistry Laboratories.[16] Also in USA, a document from the National Kidney Disease Education Program (NKDEP) strongly encouraged clinical laboratories to automatically report eGFR whenever serum creatinine is ordered as a practical way to identify people with CKD who might otherwise go untreated, and to monitor those with risk factors for CKD. The document recommended that for most patients, eGFR by MDRD equation is more accurate than 24 hr creatinine clearance for adults except when the patient's basal creatinine production is expected to be very abnormal.[17]

Pitfalls in the interpretation of eGFR have to be considered particularly with the expected limitation in the analytical performance of creatinine measurement especially when serum creatinine is near the normal range.[18,19] Accordingly, the NSF for Renal Services and Kidney Disease recommended reporting the exact numerical values of eGFR till the value of 90 mL/min/1.73m^2, with values above this level should be reported only as >90 mL/min/1.73m^2. However, for eGFR values in the ranges ≥90 and 60-89 mL/min/1.73 m^2, then CKD stage 1 and stage 2 respectively will be considered to exist only when there is an additional clinical or laboratory evidence of structural abnormality, as determined by renal ultrasound (such as polycystic kidney disease) or a functional abnormality (such as persistent proteinuria or microscopic haematuria).[16] If there are no such abnormalities, GFR of ≥60 mL/min/1.73m^2 is not regarded as abnormal. This recommended system of routine eGFR reporting has been followed mostly in UK and Australia. On the other hand, the American NKDEP recommends reporting GFR values till the value of 60 mL/min/1.73m^2 and values >60 mL/min/1.73m^2 will be reported as >60 mL/min/1.73m^2 and not as the exact number for the reasons stated above.[17] Both guidelines consider CKD stage 3-5 at eGFR <60 mL/min/1.73m^2 which are of more clinical implications and at which levels the creatinine measurement is more precise and accurate. This recommended system of reporting is mostly followed in USA and Canada.

Reporting eGFR has to be interpreted with caution in acute renal failure, pregnancy, oedematous states, muscle wasting disorders, amputees, paraplegics, morbid obese, and malnourished people.[8,16] The most recent edition of the British National Formulary (BNF) has replaced reference to creatinine clearance with eGFR. Accordingly, for most drugs for adults aged >18 years with average body surface area, eGFR.MDRD can be used for drug dosage adjustment instead of creatinine clearance. Exceptions include potentially toxic drugs with small safety margin and patients at extreme of age,[20] a recommendation that was supported by Stenvens *et al*.[21] The MDRD equation should not be used in children, where other formulae such as Counahan and Schwartz equations that require knowledge of height (length) of the child are available. Whilst these estimates may be used in certain settings, however routine reporting of eGFR in children by laboratories may not be easily recommended.[22-24]

Literature search conducted in Pubmed for the period from January 1999 to December 2011 for the studies in which MDRD formula was cited or referred revealed 1224 publications which reflects the impact of awareness and growing implementation of this formula in Medicine. Currently, there is no doubt that eGFR. MDRD is considered to be an integral test in renal function assessment and has growing role in alerting the clinicians about the renal function status. Accordingly, care of CKD has been shifted from Secondary Care to being Primary Care priority. The interpretation of eGFR gained wise approach by requesters in that the numerical value of the result may reflect the proportional function of the intact functioning nephrons. This means that if a patient has an eGFR of 15 mL/min/1.73m^2 then almost 15% of the renal function may be intact. This is contrary to serum creatinine whose reference range varies greatly depending on age, sex, gender and muscle mass, making many interpreters unaware and inexperienced in its interpretation particularly when the level is slightly elevated, at which level it really reflects significant renal impairment.[9,10]

The rapid implementation, wide acceptance and improved awareness in the interpretation of eGFR compared with serum creatinine are not without controversy or critical concern at least from the clinical viewpoint. It has been observed particularly in the last few years following the introduction of eGFR reporting that there is an increase in the number of people in the Primary Care recognized to have CKD as well as increase in patient's referral to nephrologists. In UK, the Quality and Outcomes Framework (QOF) data revealed that there is an increase in the prevalence of stage 3-5 CKD in adults to 4% in 2008/2009 compared with 3.7% in 2007-2008 and 3% in 2006-2007.[20] Also, in UK in 2006-2008, about 40% of patients with expected CKD3-5 were recognized in the primary care.[25] In Alberta, Canada, a laboratory registry to track nephrology consultations before and after the implementation of eGFR reporting revealed an associated increase in nephrology referrals particularly in individuals with more severe CKD, middle-aged and elderly (in whom lowered GFR is not easily detected by increased serum creatinine alone because of the low creatinine production) and those with comorbidities.[26] Also, in a Canadian population- based intervention for data from more than 8 million adults over 10-year comparing clinical outcome for the period reporting serum creatinine alone or in combination with eGFR revealed an increase in the number of patients seen in consultation by nephrologists after eGFR reporting by 24%, the greatest increases were in women (39%) and in those aged ≥80 years (58%).[27] On the other hand, an analysis based on the NANHES III and Medicare databases showed that CKD care may be still suboptimal,[28] with other surveys suggest that primary care providers and internal medicine residents may be not familiar with KDOQI guidelines.[29-31]

Existence particularly of early stages of CKD in many of the

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individuals screened is under concern by many nephrologists. Therefore, the need for more efficient and accurate screening tests was addressed as the currently used eGFR.MDRD method is not without dubious value. It performs better at lower GFR but it is limited by underestimating the GFR at higher values and so may overestimate individuals as having stage 1-3 CKD. The equation based eGFR does not consider in depth the expected normal age and gender decline in GFR which may result in many elderly subjects particularly those not at risk to be labeled as having CKD. Whether CKD should be considered or staged based on modest decline in eGFR in elderly subjects without other risk factors may be debatable. Hence targeted screening of at risk individuals will be more clinically and cost-effective approach, a message that could be easily transmitted through public health programs.[32-35]

To improve the aforementioned confounding factors and pitfalls particularly the limited precision and systematic underestimation of the eGFR at higher values, the MDRD equation was revisited by its original authors, Levey *et al*[36] in 2009. Data from 10 studies (n=5504) comparing serum creatinine with iothalamate clearance was pooled to modify MDRD equation into a new equation: the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation which was then validated against data pooled from 16 studies (n=3896). The new equation was evaluated down to serum creatinene of 62 µmol/L (in women) and 80 µmol/L (in men). CKD-EPI was found to be more accurate estimate of GFR in the range of low serum creatinine and higher GFRs. The equations are as follows:

For female with creatinine < 62 µmol/L:
$$\text{eGFR } (\text{mL/min/1.73m}^2) = 144 \times (\text{Cr}/61.6)^{-0.329} \times (0.993)^{\text{Age}}$$
For female with creatinine > 62 µmol/L:
$$\text{eGFR } (\text{mL/min/1.73m}^2) = 144 \times (\text{Cr}/61.6)^{-1.209} \times (0.993)^{\text{Age}}$$
For male with creatinine < 80 µmol/L:
$$\text{eGFR } (\text{mL/min/1.73m}^2) = 141 \times (\text{Cr}/79.2)^{-0.411} \times (0.993)^{\text{Age}}$$
For male with creatinine > 80 µmol/L:
$$\text{eGFR } (\text{mL/min/1.73m}^2) = 141 \times (\text{Cr}/79.2)^{-1.209} \times (0.993)^{\text{Age}}$$

Levey *et al*[31] reported that CKD-EPI yielded lower estimated prevalence of CKD than the MDRD (11.5% versus 13.1%), mainly because of a lower estimated prevalence of stage 3 CKD. They suggested the CKD-EPI equation to replace the MDRD equation in clinical use. In UK, a recent study was conducted by Carter *et al*[37] to assess the MDRD and CKD-EPI equations in a large adult UK population (n = 561,400). CKD-EPI produced higher GFR and lower CKD estimates, particularly among 18-59 year age groups with MDRD eGFRs of 45-59 mL/min/1.73m^2 (Stage 3A CKD). However, at ages >70 years there was very little difference between the equations, and among the very elderly CKD-EPI may actually increase CKD prevalence estimates. The median CKD-EPI GFR was significantly higher than median MDRD GFR (82 vs. 76 mL/min/1.73m^2), p <0.0001). Although statistically significant at all age groups the difference diminished with age. The age-adjusted population prevalence of CKD Stages 3-5 was lower by CKD-EPI than by MDRD (4.4% vs. 4.9%).[37] Despite the advantages of CKD-EPI formulae, in UK the MDRD equation is still universally used however there are reports from laboratories in the USA with implementation of CKD-EPI equation.[33,38] In Australia, the application of the CKD-EPI equation in the Australian, Diabetes, Obesity and Lifestyle (AusDiab) Study also yielded a lower estimated prevalence of CKD compared with the MDRD equation, namely 11.5% compared with 13.4%.[39] Application of CKD-EPI equation together with the other diagnostic tools in renal medicine will further improve the detection and management of patients with CKD.

Other Markers of Chronic Kidney Disease

Of additional importance in this regard is the role of the presence or absence of albuminuria in the stratification of all stages of CKD, including diagnosing, staging and monitoring as has been recommended in the many guidelines.[32] NICE has recommended for detecting proteinuria to measure random urine albumin:creatinine ratio in preference to other tests of proteinuria including protein:creatinine ratio, 24 hour urinary total protein and reagent dipstick strip testing.[3] Both reduced eGFR and albuminuria are strong predictors for cardiovascular events with clinical trials showed that the use of angiotensin-converting enzyme inhibitors or angiotensin receptors blockers slowed the decline in the eGFR.[40] In addition, efforts should be considered in the development and validation of other renal function tests that in parallel with eGFR reporting will focus on improving the outcome in the diagnosis and management of CKD. The near future may show an analytical improvement in creatinine measurement with its impact in improving the sensitivity of the assay and hence eGFR reporting. Also, implementing and evaluating other markers of renal function such as measurement of serum Cystatin C and other markers of kidney injury may add to the diagnostic and management role of renal function testing in renal medicine.[41-43]

Conclusion

During the last decade, there has been an increasing interest in the guidelines from many professional medical societies towards the classification and management of CKD. Despite its limitations, the implementation of eGFR reporting especially in high-risk patients has significantly contributed in the early recognition of CKD that allows the provision of appropriate therapy and so alerting the clinicians for the impact of chronic diseases on kidney function. There are many equations for calculating eGFR from serum creatinine in adults without the need for urine collection. The need of Cockcroft and Gault equation for body weight has limited its routine application in laboratory practice. However, the ease of MDRD equation which does not require body weight for eGFR calculation has contributed in its rapid implementation and acceptance in clinical medicine with recommendation towards its routine reporting together with serum creatinine as a renal function profile. Following the introduction of eGFR reporting, there has been a paradigm shift from CKD being viewed as secondary care condition to being primary care priority with an increase in the number of people in the primary care recognized to have CKD, in the prevalence of CKD and in patient's referral to nephrologists. However, the equation still has its own controversy particularly in under-estimating GFR at low-normal level of serum creatinine, in diagnosing stage 1-3 CKD, in women, and in the elderly. These limitations appear to be improved by the new CKD-EPI equation that was described by the same authors of MDRD equation Levey *et al* who suggested the CKD-EPI equation to replace the MDRD equation in clinical use. Compared with MDRD, the CKD-EPI produces higher GFR and lower CKD estimates, particularly among 18-59 year age groups with eGFRs of 45-59 mL/min/1.73m^2 (stage 3A CKD). Although the MDRD equation is still universally followed worldwide, however utilization of CKD-EPI in laboratory practice may be expanded in the next few years. It is also important to ensure that all health care professionals, both generalists and specialists, understand the importance of the early diagnosis of kidney disease. Physicians should be made especially aware that older patients and those with diabetes, hypertension, or cardiovascular disease should be systematically screened for the presence of CKD, a message that could be easily transmitted through public health programs. In addition, there is a growing awareness about the role of albuminuria/proteinuria in the stratification of all stages of CKD. Recently measurement of albuminuria has been recommended in many guidelines, as both reduced eGFR and albuminuria are strong predictors for cardiovascular events and progression of renal disease. Finally, continuous efforts should be considered in the development and validation of the renal function tests including analytical improvement in creatinine measurement with its impact in improving the assay sensitivity and hence eGFR reporting. Also, implementing and evaluating other markers of renal function such as measurement of serum Cystatin C and other markers of kidney injury may add to the diagnostic and management role of renal function testing in renal medicine.

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