

Automated estimated GFR reporting: A new tool to promote safer prescribing in patients with chronic kidney disease?

KPG Harris¹
Bernie Stribling²

¹University Hospitals of Leicester NHS Trust; ²East Midlands Renal Network

Abstract: A number of drugs rely on the kidney for excretion and thus require their dose to be modified in any patients where there is renal impairment. Others are nephrotoxic and should be avoided completely in patients with renal disease. Traditionally clinicians have had to rely on serum creatinine to assess renal function but this may not accurately reflect the kidney function of an individual since its level also depends on muscle mass. In particular elderly females may have significant impairment of renal function despite a normal or near normal serum creatinine. The advent of automated reporting of estimated glomerular filtration rate (eGFR) provides the clinician with simple, easily understood and readily available measurement which more accurately reflects a patient's renal function. In particular eGFR allows the clinician to readily identify and stratify patients with chronic kidney disease (CKD) and can allow a more rational and safer approach to prescribing in this group of high risk patients. This commentary suggests that national prescribing formularies should use eGFR to provide consistent advice about the appropriate dose adjustment and avoidance of potentially toxic drugs at various stages of CKD. Such an approach may prove invaluable in improving prescribing in CKD and avoiding drug toxicity in this group of patients.

Keywords: eGFR, chronic kidney disease, prescribing

The "gold standard" measurement for assessment of renal function is glomerular filtration rate (GFR). The normal range is 90–120 ml/min/1.73 m² and hence it provides easy to interpret information for the doctor and patient on the degree of renal impairment since it approximately equates to the percentage of kidney function remaining.

The international 5 stage classification of chronic kidney disease (CKD) developed by the US National Kidney Foundation in their Kidney Disease Outcomes Quality Initiative (KDOQI 2002) (Table 1) has now been widely adopted by nephrologists. The classification is based on the level of GFR for stages 3–5, although it is important to recognize that stages 1 and 2 can only be defined if there is other evidence of kidney damage such as urinary sediment abnormalities (proteinuria and or hematuria) or structural abnormalities.

Knowledge of a patient's GFR allows the dosing of any drug which relies on a renal route of excretion to be adjusted appropriately and in addition requires those drugs with predictable adverse effects on renal function to be avoided when renal function is already poor. Although a number of techniques for the accurate measurement of GFR have been described, in practice, these are expensive and complex to perform, requiring infusions of appropriate chemical or radiolabeled substances (such as inulin of EDTA) and multiple blood sampling. Thus, such techniques remain essentially a research tool and are not used in clinical practice. Clearance of endogenous creatinine (Creatinine Clearance) is can be used as a surrogate marker of GFR since creatinine is

Correspondence: KPG Harris
John Walls Renal Unit, Leicester General Hospital, Leicester LE54PW, UK
Tel +44 116 258 4195
Fax +44 116 258 4764
Email krgh1@le.ac.uk

Table 1 The stages of CKD as defined in the KDOQI classification. CKD is defined as either kidney damage of a GFR of less than 60 ml/min/1.73 m² for more than 3 months

Stage	GFR	Description
1	> = 90	Kidney damage with normal or increased eGFR
2	60–89	Kidney damage with mild eGFR fall
3	30–59	Moderate fall in eGFR
4	15–29	Severe fall in eGFR
5	<15 or renal replacement therapy	Established renal failure

mainly handled by glomerular filtration. However it requires the collection of timed urine samples (usually 24 hours) with simultaneous blood sampling and is time consuming to perform and often difficult for the patient to perform accurately. In addition at low GFRs the contribution of tubular and extrarenal excretion of creatinine to the measurement becomes significant and leads to Creatinine Clearance significantly overestimating GFR. It should also be noted that even so called “gold standard” measurements of GFR can have up to a 20% day to day variability.

In routine clinical practice, clinicians have relied on serum creatinine to assess renal function. However the serum creatinine level depends on only on renal function but also on muscle mass since creatinine is derived from muscle creatine. It cannot therefore, in isolation, accurately reflect the kidney function of an individual. For a given level of renal function, serum creatinine will vary according to factors such as age, sex, body mass and ethnic origin since these are surrogate markers of an individual’s muscle mass. Thus an elderly female with significant CKD (stage 3) may still have a creatinine in the “normal range” because of low muscle mass and low creatinine production.

Since the measurement of GFR is not practical for routine clinical use, many specialist renal and pathology societies including those in the US, UK and Australasia now recommend the adoption of automated reporting of formula based estimations of GFR (estimated GFR or eGFR). It should always be remembered that such equations are derived from studies of typical populations and therefore may have their limitations when applied to individuals in whom creatinine production is atypical or in whom the volume of distribution of creatinine concentration may be altered (see Table 2). They may show decreased accuracy in patients with high GFRs (eg, the young healthy) and in the elderly and in children. It is also particularly important to remember that eGFR was validated as a measure of renal function in patients with stable

chronic kidney disease and therefore should not be used to assess of renal function in acutely unwell patients with acute kidney injury or changing renal function. However with these caveats in mind, the inaccuracies inherent in eGFR are still likely to be less than when using serum creatinine alone.

The widespread introduction of automated eGFR reporting has made the true prevalence of CKD readily apparent to clinicians. Whilst this was the intention, concern has been expressed that because of the potential for formulae to underperform when the true GFR is near normal and at extremes of age, normal elderly patients may be inappropriately labeled with a chronic disease. In areas where automated eGFR reporting has been introduced nephrology units generally experience a significant increase in referrals; however with time once the wave of newly discovered patients have been seen, new incident referral rates tend to fall back to baseline especially when clinical guidelines which define those likely to benefit from nephrology advice are rigorously applied (for example the UK Guidelines for Identification, Management and Referral of adults with CKD).

A number of such formulae are available (at least 46) but for adults the abbreviated MDRD formula (Levy 2000) has been most widely adopted since it is the most practical relying only on creatinine, age and sex in the calculation. This allows it to be reported automatically by laboratories when serum creatinine is requested, without additional information or measurements being required (the clinician is required to apply a correction of 1.21 if the patient is of black African extraction). The MDRD formula has been shown to perform well in a number of studies of different patient populations and typically outperforms other formulae when compared to “gold standard” measures of GFR. To improve accuracy of the MDRD formula and allow comparison between results generated in different laboratories it is important that the creatinine assay has been standardised to that used by those who developed the MDRD equation (or an appropriate

Table 2 Situations in which creatinine production or volume of distribution may be atypical and hence eGFR be unreliable

- Muscle wasting disease states
- Amputees
- Malnourished patients
- Edematous states
- Pregnancy
- High or low dietary intake of creatinine or creatine
- Extremes of body size
- Extremes of age
- Particular ethnic groups

correction applied). Many national quality assurance schemes for pathology are undertaking such standardization ensuring the MDRD formula is appropriately corrected for different local creatinine assays; for these reasons automated reporting of eGFR is to be preferred rather than the clinician calculating eGFR from the reported creatinine. The MDRD formula typically underestimates GFR in patients with higher levels of kidney function, but such a bias is less important when monitoring patients with impaired renal function. It is important to remember that the MDRD formula has only been validated in adults and that alternative formulae must be used for children (of which the Schwartz and Counahan-Barratt equations are examples).

There are a number of methodological differences between the various formulae. For example the MDRD formula was derived by comparison with measured GFR and reports eGFR corrected for body surface area whereas the Cockcroft and Gault formula was derived from creatinine clearance and is not corrected for body surface area. Most drug information sheets recommend drug dosage adjustment based on creatinine clearance, without 'normalisation' for body surface area: thus use of normalised formulae could lead to prescription of inappropriately higher doses for smaller patients. However, it is unlikely that such differences would result in clinically important differences in drug doses in stage 3 CKD. In situations where dosing accuracy is more critical (when prescribing chemotherapeutic agents for example) sound clinical judgement must be applied and the use of formula to adjust drug doses individualised based on the best available source of evidence; where necessary direct measurement of the GFR should be undertaken.

Prescribing guidelines and drug information leaflets recommend dose adjustment in renal impairment for drugs which are either excreted or metabolized by the kidney. For drugs with either minor or no dose related side effects any required dose manipulation may be small. Others, especially those with potential for nephrotoxicity may need to be avoided altogether in advanced kidney disease. However, despite the changes in nephrology practice with the adoption of the widely accepted KDOQI classification of CKD, many formularies continue to recommend dose adjustment according to arbitrary grades of renal impairment (mild, moderate, severe) or serum creatinine levels. The advent of eGFR reporting has the potential to allow the clinician to adopt a more logical and accurate approach to the use of drugs in patients with CKD and in particular has the potential to unmask significant renal impairment in groups of patients where it might previously have gone unnoticed as the serum

creatinine was within or nearly within the "normal range". eGFR is not a perfect solution as it is an estimate based on population averages: as such there will still be some situations where actual assessment of GFR would be preferable (especially when using drugs with a high potential for toxicity and narrow therapeutic range).

Some practical examples of how eGFR may help improve medicines management are listed below.

1. A number of drugs are best avoided completely in patients with CKD because of their predictable adverse effects. The commonest example is NSAIDs which have the potential to decrease GFR by removing the influence vasodilator prostaglandins from within the kidney. If the GFR is near normal this may be of little or no clinical significance. However, in patients advanced CKD (certainly stage 4 and non dialysis dependent stage 5) the prescription of NSAIDs should be avoided. Yet most nephrologists will have seen patients precipitated onto dialysis at least in part due to inadvertent prescription of a NSAID to a patient who had unrecognized advanced CKD. Such an adverse event may be particularly likely when the NSAID is prescribed to a patient with CKD who has co-existent volume depletion, heart failure or sepsis. Automated eGFR reporting may help avoid this unmasking the true degree of renal impairment. In addition if it were linked to an "intelligent" computer aided prescribing system, the clinician attempting to prescribe a NSAID to a patient with advanced CKD could have it automatically flagged that such a prescription might be undesirable. Then if after careful risk benefit assessment a NSAID were to be prescribed careful monitoring of renal function could be undertaken.
2. Some drugs should be discontinued if they adversely affect renal function. Angiotensin converting enzyme inhibitors (ACEis) and Angiotensin receptor blockers (ARBs) fall in to this category. ACEis and ARBs may result in an unacceptable fall in GFR in patients with renal artery stenosis and if it occurs should prompt further investigation for this condition. Traditionally advice about ACEi and ARB usage has been given in terms of arbitrary changes in serum creatinine levels. However a more logical approach is to suggest discontinuation of the drug and/or referral for further investigation if a certain percentage fall in estimated GFR occurs after initiation or dose increase (>15% may be an appropriate threshold).
3. The prescribing advice for some drugs suggests they should be avoided if the patient has a serum creatinine value above a certain value. As outlined previously this will not produce a consistent approach as a given

serum creatinine level could reflect differing levels of renal function depending on the patient's age, sex and race. For example in the UK the National formulary and professional advisory bodies state that "Metformin is contraindicated in people with renal impairment (serum creatinine greater than 130 $\mu\text{mol/L}$).". However, a serum creatinine of 130 $\mu\text{mol/L}$ in a 60 year old white female would equate to an eGFR of 37 ml/min/1.73 m² and CKD stage 3. However the same creatinine in a 20 year old black man equates to an eGFR of double that at 79 ml/min/1.73 m² and CKD stage 2. Thus by adopting an arbitrary cut off for the use of this drug based on creatinine has produced an inconsistent result: either one group has been potentially deprived of its benefits unnecessarily or alternatively (but less likely) another group has been exposed to potential toxicity.

4. A number of drugs require dose adjustment (reduction) when renal function is impaired. Many antimicrobials fall in to this category. The use of vague terms such as "reduce the dose in mild or moderate renal impairment" is generally unhelpful to the clinician and leads to an inconsistent approach. eGFR offers a more objective assessment of the level of renal function and therefore the potential to develop clear and consistent guidance for the dosing of this group of drugs. There would be reduced potential for toxicity, no loss of therapeutic effect and the potential for cost savings as a result of reduced doses or dosing frequencies. Although eGFR has its own incon-

sistencies it is sufficiently robust to be used in practice for any drug with a broad therapeutic window and few dose related side effects.

In conclusion eGFR reporting offers considerable advantages to the prescribing clinician. It provides for the first time a simple, easily understood and readily available tool to allow the identification and stratification of patients with CKD. It allows a more accurate risk assessment for prescribing in CKD patients and a more rational approach to prescribing, including appropriate dose adjustment and avoidance of potentially toxic drugs. There is an urgent need for national prescribing formularies to embrace the KDOQI classification of CKD and provide consistent advice about the use of drugs at various stages of CKD and levels of eGFR. Such an approach may prove invaluable in improving prescribing in CKD and avoiding drug toxicity in this group of patients.

References

- K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. 2002. *Am J Kidney Dis*, 39(2 Suppl 2):S1–246.
- Levey AS, Greene T, Kusek JW, et al. 2000. A simplified equation to predict glomerular filtration rate from serum creatinine. *J Am Soc Nephrol*, 11:155A.
- Royal College of Physicians and the Renal Association 2006. Chronic kidney disease in adults: UK guidelines for identification, management and referral [online]. URL: <http://www.renal.org/CKDguide/full/UKCKDfull.pdf>