Position Statement

Chronic Kidney Disease and Automatic Reporting of Estimated Glomerular Filtration Rate: A Position Statement

The Australasian Creatinine Consensus Working Group

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Abstract

- The systematic staging of chronic kidney disease (CKD) by glomerular filtration measurement and proteinuria has allowed the development of rational and appropriate management plans.
- One of the barriers to early detection of CKD is the lack of a precise, reliable and consistent measure of kidney function.
- The most common measure of kidney function is currently serum creatinine concentration. It varies with age, sex, muscle mass and diet, and interlaboratory variation between measurements is as high as 20%.
- The reference interval for serum creatinine concentration includes up to 25% of people (particularly thin, elderly women) who have an estimated glomerular filtration rate (eGFR) that is significantly reduced (< 60 mL/min/1.73m^2).
- The recent publication of a validated formula (MDRD) to estimate GFR from age, sex, race and serum creatinine concentration, without any requirement for measures of body mass, allows pathology laboratories to "automatically" generate eGFR from data already acquired.
- Automatic laboratory reporting of eGFR calculated from serum creatinine measurements would help to identify asymptomatic kidney dysfunction at an earlier stage.
- eGFR correlates well with complications of CKD and an increased risk of adverse outcomes such as cardiovascular morbidity and mortality.
- We recommend that pathology laboratories automatically report eGFR each time a serum creatinine test is ordered in adults.
- As the accuracy of eGFR is suboptimal in patients with normal or near-normal renal function, we recommend that calculated eGFRs above 60 mL/min/1.73m^2 be reported by laboratories as "> 60 mL/min/1.73m^2", rather than as a precise figure.

Chronic kidney disease (CKD) is a morbid condition that is common and may be preventable. In the general Australian community, there is evidence of at least one indicator of CKD (proteinuria or reduced kidney function) in about 16% of adults aged over 25 years.[1] CKD progresses to end-stage kidney failure at a rate that requires about 1900 Australians each year to commence renal replacement treatment — either dialysis or transplantation.[2] Furthermore, in people with CKD there is actually a 20-fold greater chance of death (mainly from cardiovascular disease) than of starting renal replacement therapy.[3] However, CKD is frequently asymptomatic, and, although in some instances it can be detected by the presence of proteinuria, many afflicted people have significant reduction of kidney function without overt urinary abnormalities. Therefore, a reliable means of readily assessing the early stages of reduced kidney function is a priority.

The diagnosis and management of CKD has been facilitated in recent years by the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines of the US National Kidney Foundation. The K/DOQI guidelines advise that CKD can be defined and appropriately managed by a staging approach that relies on estimating the extent of kidney damage based on the degree of proteinuria and impaired kidney function, assessed as a reduction in the glomerular filtration rate (GFR).[4]

The most common measure used to assess overall kidney function is the serum creatinine concentration. Interpretation of this index is complicated, as it is inversely proportional to the GFR and varies between individuals based on differences in age, sex and muscle mass. Using serum creatinine concentrations to determine an absolute level of kidney function, including distinguishing normal from abnormal function in the individual patient, is inherently difficult. The broader use of serum creatinine concentration as a tool to increase the detection of asymptomatic CKD is therefore problematical.

GFR is widely accepted as the best measure of kidney function, yet in clinical practice beyond nephrology it is infrequently utilised. The main impediment to its regular clinical use has been the perception that it was necessary to estimate GFR by performing a creatinine clearance test that is dependent on a timed urine collection (usually 24 hours). More recently, calculating estimated GFR (eGFR) using an empirical mathematical formula has been encouraged through the provision of handheld or desktop semi-automated calculators designed for this purpose. The Cockcroft– Gault equation is the most frequently used eGFR formula in Australia, where a general population study has shown that 11.3% of adults have a Cockcroft–Gault eGFR below 60 mL/min/1.73m^2 (the threshold value for CKD).[1] There are now at least 46 different equations for estimating GFR, but most (including the Cockcroft– Gault equation) require additional information, such as a measure of body surface area (based on height and/or weight measurements), leading to additional complexities that limit the wider use of this approach. There are recognised difficulties associated with collecting body size measurements (e.g. errors in measurement and transcription), and, as pathology laboratories cannot ensure the quality of these variables, they are often hesitant to report eGFR using these formulas.

The possibility that pathology laboratories might routinely report an eGFR derived from the serum creatinine concentration has recently become feasible with the development of a formula whose only variables are age, sex, race and serum creatinine concentration. Most importantly, it does not require body surface-area measurements. This formula, the "abbreviated MDRD equation" (named after the US Modification of Diet in Renal Disease Study)[5], has been validated in many clinical situations. However, the adjustment for race in the MDRD equation is limited to "African-American", which may affect the formula's applicability to the Australasian population. In particular, the MDRD formula has not yet been validated in Aboriginal and Torres Strait Islander populations. Moreover, although there is evidence that automated laboratory reporting leads to greatly enhanced detection of CKD by health professionals,[6] there is no high-level clinical evidence that this in turn leads to improved clinical outcomes. A reanalysis of the AusDiab study data recently showed that 7.5% of the Australian adult population had an eGFR (based on the abbreviated MDRD formula) of < 60 mL/min/1.73m^2 (Associate Professor Steve Chadban, Nephrologist and Director of Kidney Transplantation, Royal Prince Alfred Hospital and University of Sydney, personal communication). The K/DOQI and UK Renal Association guidelines recommend automatic reporting of eGFR from serum creatinine measurements, and advocate using the MDRD formula for this purpose.[4,7,8]

Because of these developments, an Australasian Creatinine Consensus Working Group (see end of Position Statement), met in November 2004 to develop recommendations on the desirability of automatic reporting of an eGFR from each serum creatinine measurement performed in pathology laboratories. The opportunity was taken to address issues relating to inconsistencies in the measurement and reporting of serum creatinine concentration that might affect its use for calculating eGFR.

The Working Group meeting was sponsored by the Australasian Association of Clinical Biochemists, the Australian and New Zealand Society of Nephrology, Kidney Health Australia and the Royal College of Pathologists of Australasia, and was attended by 21 representatives of these organisations. The following recommendations emanated from the meeting. All resolutions were endorsed unanimously, with the exception of Recommendation 6, where there was one abstention. The Australian Diabetes Society has also endorsed the recommendations.

Recommendations

A. Measurement of serum creatinine concentration and its use to calculate eGFR

1. Serum creatinine assays should be considered acceptable with respect to bias and precision if their results lie within ±15% of values calculated by the international reference method (isotope dilution mass spectrometry).

The estimation of GFR from serum creatinine levels contains a degree of imprecision. Variations of eGFR from the direct measurement of GFR arise from a number of factors, including variability in serum creatinine measurements and the imperfect nature of the estimation equation. For example, the US National Kidney Disease Education Program (NKDEP) has estimated that variability of ±15% may be attributed to the MDRD equation itself. The NKDEP has set a goal of overall accuracy of ±30% for the estimation of GFR, and thus, by allowing for ±15% variability inherent in the estimation equation, recommends that the total error in serum creatinine measurement should be less than ±15%.

In accepting this quality specification, an important issue is assigning a target against which to compare assay performance. The MDRD formula was derived using a serum creatinine assay from Beckman Coulter run on a CX3 analyser, and assays that produce results within ±15% of this type of assay would thus fulfil the accuracy criterion. The CX3 creatinine assay is known to have a small positive bias compared with the recognised international reference method for creatinine measurement (isotope dilution mass spectrometry [IDMS]). As most current routine serum creatinine assays produce

results equal to or higher than the IDMS reference method (for results within the reference interval 40 – 110 μmol/L), assays producing results within ±15% of methods aligned with IDMS will show a total error compared with the CX3 method of less than ±15%, and therefore also satisfy the criterion. In accepting the accuracy criterion, it is hoped that manufacturers will be encouraged to develop creatinine assays that are more closely aligned with the IDMS reference method to allow improved method standardisation in the future.

2. Commercially available creatinine assays should meet the accuracy criterion for serum creatinine levels >100μmol/L.
A review of the status of serum creatinine measurement in Australia and New Zealand using data from national[9] and international[10] sources and local sample-sharing studies (Dr Graham Jones, Staff Specialist in Chemical Pathology, St Vincent's Hospital, NSW, personal communication) was presented to the Working Group. These studies indicate that, at serum creatinine concentrations of about 100 μmol/L, creatinine assay results supplied by the major manufacturers generally meet the total error requirement of ±15% deviation from the Beckman Coulter method. At higher creatinine concentrations, the assays meet this criterion without difficulty, but at lower concentrations, there is some variation in achieving this standard. Professional bodies must develop methods for confirming that assays meet the criterion, and laboratories must ensure that their creatinine assays conform to these requirements.

B. Reporting of serum creatinine levels

3. Serum creatinine levels shall be reported in μmol/L.
The formal application of the International System of Units (SI) recommends using whole numbers rather than numbers frequently less than one. By this standard, the SI units for serum creatinine concentration should be μmol/L. A recent international survey of pathology reporting indicated that all countries using SI units (except Australia and New Zealand) reported creatinine levels in μmol/L.[10] In Australia and New Zealand, laboratories are currently divided about equally between using mmol/L or μmol/L as the unit. Conversion of all laboratories to μmol/L as the reporting unit is considered to be a useful step in minimising confusion in clinical interpretation.

4. Serum creatinine concentrations determined to the nearest 1μmol/L shall be used for all eGFR calculations.
The estimation of GFR from serum creatinine level should be performed routinely by laboratories using data rounded to the nearest 1 μmol/L. Measurement of serum creatinine level to the nearest 1 μmol/L allows optimal quality control of such assays, especially for results within the reference interval. Adopting the principle that calculations should be made on raw (unrounded) data where possible, it is recommended that the calculation of eGFR should be performed using serum creatinine measurements reported to this level of precision.

5. Laboratories should have data on precision of serum creatinine measurements near 100mol/L available, and also the rationale for their reported reference interval.
Serum creatinine concentrations associated with a calculated GFR at the important 60 mL/min/1.73m^2 decision point are between 80 μmol/L and 120 μmol/L, depending on the age and sex of the patient. To provide information on the assay performance in this range, an internal quality control sample should be run with a creatinine concentration near 100 μmol/L. These data, together with information on biological variation, should be available to clinicians when requested.

C. Reporting of eGFR

6. Estimates of GFR shall be reported in mL/min or, if corrected for body surface area, in mL/min/1.73m^2.
The MDRD formula yields an eGFR normalised to 1.73m^2 body surface area. Adjusting for body surface area is necessary when comparing a patient's eGFR with normal values or when determining the stage of CKD. However, an uncorrected eGFR may be preferred for clinical use in some situations, such as drug dosing. To revert to an uncorrected eGFR, the result from the MDRD-derived eGFR should be multiplied by the individual's body surface area, and divided by 1.73, using the following formula:

BSA = $W^{0.425}$ x $H^{0.725}$ x 0.007184/1.73
where BSA = body surface area (m^2), W = weight (kg),
H = height (cm)
Uncorrected eGFR = GFR estimate (mL/min/1.73 m^2) x BSA

In practice, adjusted GFR estimates are adequate except in patients with a body size that is very different from the average.

It should be noted that recommendations for drug-dosing adjustments for patients with reduced kidney function are currently based on the Cockcroft–Gault formula, and this result may differ significantly from the MDRD-derived eGFR.[11]

In recommending the unit of mL/min, it is recognised that this deviates from the SI unit of time (the second). However, as the overwhelming majority of clinical interpretive information (both Australian and worldwide) uses the unit mL/min, this unit is accepted in order to promote standardisation and remove a source of potential confusion.

D. Automatic reporting of eGFR from serum creatinine level

7. An eGFR based on the abbreviated MDRD formula shall be automatically calculated for every request for measurement of serum creatinine concentration in people aged 18 years.

The primary reasons for the recommendation are as follows:

- Kidney function is poorly deduced from the serum creatinine concentration alone;
- Serum creatinine concentration is an imprecise measurement of kidney function, as it varies according to age, sex, muscle mass and diet;
- The use of serum creatinine concentration alone to assess kidney function results in undiagnosed cases of CKD, as up to 25% of results may lie within the accepted reference interval yet translate to an abnormal eGFR (< 60 mL/min/1.73m^2);[12]

The abbreviated MDRD formula (Box) was recommended on the basis of the following factors:

- MDRD is a thoroughly validated equation in adults;[12,14]

The abbreviated MDRD equation[13]

eGFR = 186 x ([S_{CR}/88.4]$^{-1.154}$) x (age)$^{-0.203}$ x (0.742 if female) x (1.210 if African-American)

where eGFR = estimated glomerular filtration rate (mL/min/1.73m^2), SCR = serum creatinine concentration (μmol/L), and age is expressed in years.

An automated calculator for MDRD-based eGFR can be found at <http://www.kidney.org.au>.

MDRD = Modification of Diet in Renal Disease.[5]

- Direct comparison of the MDRD equation with other equations such as the Cockcroft–Gault equation and to results from 24-hour urine collections have shown the MDRD equation to be superior for estimating GFR, particularly in the range GFR < 60 mL/min/1.73m^2 ;[4,15]

- There is no requirement for additional information (e.g. measurements of body surface area) beyond that already collected by pathology laboratories.

As the MDRD formula has not been validated in children, its use should be restricted to people over 18 years of age.

8. eGFR values over 60 mL/min/1.73m^2 should be reported as "> 60mL/min/1.73m^2", rather than as a precise figure.

The recommendation that a value of eGFR calculated to be above 60 mL/min/1.73m^2 should not be reported as a precise figure is based on:

- the less precise nature of the relationship between MDRD-derived eGFR and direct measurement of GFR (e.g. based on inulin or isotopic methods) in the higher ranges;
- the fact that the MDRD formula was initially derived from data acquired from people with CKD. Comparisons of this formula with direct measures of GFR (e.g. methods using iothalamate) in healthy people indicate a significant underestimation of measured GFR, most marked in the normal GFR range;[16]
- the greater interlaboratory variation in serum creatinine concentrations (related to calibration and choice of laboratory method) in the range of values that translate to an eGFR > 60 mL/ min/1.73m^2;
- the strong evidence that, at all ages in the adult, an eGFR < 60 mL/min/1.73m^2 correlates with complications of CKD, including anaemia, increased cardiovascular risk and death.[3,17-20]

9. Automatic reporting of eGFR may include age-related reference intervals for people aged 65 years.

The age-related decline in GFR that has been described with inulin-based GFR measurements,[21] and more recently with eGFR methods, appears to be about 8 mL/min per decade.[12] No Australian data have been published in this area. Automatic reporting of eGFR from serum creatinine concentration will likely reveal that 25% of the Australian population aged over 70 years has an eGFR <60mL/min/1.73m^2, as previously demonstrated by US data.[12] It thus seems prudent to report a reference interval for people over 70 years to guide decision-making for older age groups. The mean eGFR for people aged 70 years and over in the United States has been calculated to be 75 mL/min/1.73m^2.[22] Further work is in progress to refine the recommendations for Australia and to decide whether a qualifying statement is needed to help interpret eGFRs automatically generated for older age groups.

10. Implementing automatic eGFR reporting will require a timely educational program to ensure that information is available to help health professionals interpret eGFR values.

Comprehensive education initiatives are required to help healthpractitioners understand the limitations of the eGFR. The information they will need includes:

- an appropriate management pathway for those with an eGFR < 60mL/min/1.73m^2 (including indications for nephrologist referral);
- changes in eGFR with age;
- decreased accuracy of eGFR above 60 mL/min/1.73m^2;
- implications of body surface area for consideration of drug doses;

- decreased accuracy of eGFR in acute/unstable conditions;
- precision of eGFR result; and
- lack of applicability of eGFR to dialysis-dependent patients.

Specific clinical settings in which eGFR is not appropriate for use and GFR should be measured directly include:

- populations in which the MDRD equation is not validated (e.g. Asian people)[23] or in which validation studies have not been performed (e.g. Aboriginal and Torres Strait Islander populations);
- severe malnutrition or obesity;
- extremes of body size and age;
- exceptional dietary intake (e.g. vegetarian diet or creatine supplement;
- Disease of skeletal muscle, paraplegia, etc;
- Rapidly changing kidney function.

A concerted educational campaign is planned to coincide with the implementation of these recommendations. In addition, pre- and post-implementation audits will be undertaken to assess the impact of automatic eGFR reporting on awareness, detection and management of CKD in primary health care, as well as on nephrologist referrals. This information will also assist workforce and health resource planning.

Conclusion

Automatic reporting of the eGFR on each occasion a serum creatinine test is requested will significantly increase the likelihood of early detection of CKD and allow appropriate management. In making the conservative recommendations outlined here, we recognise the limitations of existing knowledge, including the current imprecision of creatinine measurement and the imperfections of the MDRD formula, particularly as it applies to GFR in healthy people. The restrictions and qualifications recommended should allow the benefits of this approach to be realised without causing unnecessary concern and unneeded investigations. We recognise that this is an evolving area - creatinine measurement and GFR estimation formulas are likely to improve, and alternative methods for GFR measurement will be developed. However, we believe it is vital to begin a coordinated national effort to improve the identification of patients with renal impairment, providing a firm base on which to build future developments.

Members of the Australasian Creatinine Consensus Working Group

Nagesh Anavekar (Baker Heart Institute, VIC); Renze Bais (Pacific Laboratory Medicine Services, NSW); Shane Carney (John Hunter Hospital, NSW); James Davidson (LabPlus, Auckland Hospital, NZ); Josette Eris (Royal Prince Alfred Hospital, NSW); Martin Gallagher (Canberra Hospital, ACT); David Johnson (Princess Alexandra Hospital, QLD); Graham Jones (St Vincent's Hospital, NSW); Ken Sikaris (Melbourne Pathology, VIC); Maureen Lonergan (Wollongong Hospital, NSW); Marie Ludlow (Kidney Health Australia); James Mackie (Prince of Wales Hospital, NSW); Tim Mathew (Kidney Health Australia); Steve May (Tamworth Base Hospital, NSW); Grant McBride (Southern Pathology, NSW); Matthew Meerkin (Mayne Health Laverty Pathology, NSW); Michael Peake (Flinders Medical Centre, SA); David Power (Austin Health, VIC); Paul Snelling (Royal Prince Alfred Hospital, NSW); David Voss (Middlemore Hospital, NZ); Rowan Walker (Royal Melbourne Hospital, VIC).

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