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Chronic kidney disease and automatic reporting of estimated glomerular filtration rate

A recent position statement issued by the Australasian Creatinine Consensus Working Group sparked a lively response from our readers (*Med J Aust* 2005; 183: 138-141)

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TO THE EDITOR: We were pleased to read the position statement of the Australasian Creatinine Consensus Working Group¹ recommending that laboratories automatically report estimated glomerular filtration rate (eGFR) each time a serum creatinine test is ordered in adults. We implemented this at Christchurch Hospital in March 2005 after consultation with key clinical staff. It has been well received and has resulted in a significant fall in the ordering of 24-hour urine collections.

We firstly validated the performance of the abbreviated MDRD (Modification of Diet in Renal Disease) equation² in a pilot study of 30 patients aged 40–85 years in a steady state undergoing radionuclide GFR measurement, adjusted for body surface area. The MDRD calculation showed a mean bias of $-4.2 \text{ mL/min}/1.73\text{m}^2$ (95% CI, -12.9 to $4.5 \text{ mL/min}/1.73\text{m}^2$) compared with $-7.1 \text{ mL/min}/1.73\text{m}^2$ (95% CI, -18.5 to $4.2 \text{ mL/min}/1.73\text{m}^2$) for the Cockcroft–Gault equation — thus, less bias and dispersion.

The position statement advocates measuring serum creatinine concentration to the nearest 1 mmol/L to avoid premature rounding of data in the calculation. However, other studies have suggested that this is inappropriately tight,³ and we contend that, although this is an appropriate manipulation in the calculation, it does not need to be preserved at the point of reporting, when a creatinine concentration to the nearest 10 mmol/L would be sufficient.

At our hospital, “adult” status begins from the age of 16 years, and clinicians expressed a preference that we report eGFR from this younger age. They also expressed a preference that we report actual values rather than $>60 \text{ mL/min}/1.73\text{m}^2$. Given the absence of well validated age-adjusted normative data, we elected to give a reference range of 80–120 mL/min/1.73m², while appending the comment, “GFR declines by 1 mL/min/

1.73m² per year over the age of 40 years”. Also included in a comment with every report is the caveat that eGFR is only valid under steady-state conditions and that it has not been validated for extremes of body mass or in pregnant women, non-white populations, oedematous patients or people with other complex conditions.

If the creatinine concentration exceeds an earlier value within the previous 4 days by more than +17% (a critical difference with 95% probability⁴), then an alternative comment is issued indicating that steady-state conditions are not met, although eGFR is still reported. Similar considerations regarding non-steady state apply equally to serum creatinine alone.

The position statement is helpful, but should not be regarded as rigidly prescriptive. Institutions should have the freedom to tailor the package to their own requirements, based on consultation with key clinicians.

1 The Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 2005; 183: 138-141.

2 Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Diseases Study Group. *Ann Intern Med* 1999; 130: 461-470.

3 Badrick T, Wilson SR, Dimeski G, Hickman PE. Objective determination of appropriate reporting intervals. *Ann Clin Biochem* 2004; 41: 385-390.

4 Fraser CG. Biological variation: from principles to practice. Washington, DC: AACCC Press, 2001. □

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TO THE EDITOR: I applaud the recent position statement of the Australasian Creatinine Consensus Working Group.¹ It is in line with worldwide support for the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for chronic kidney disease² expressed by the Renal Association of Great Britain and the International Society of Nephrologists as well as North American groups. However, I am concerned about universal reporting of the Modification of Diet in Renal Disease (MDRD) calculation of glomerular filtration rate (GFR) applied to pregnant women.

As described in the K/DOQI guidelines, the MDRD calculation has not been validated in pregnancy. Other formulas are available for calculating estimated GFR (eGFR) using serum creatinine level and several other variables, yet none have been accepted for use in pregnancy. A single study³ from 1994 followed 34 women with impaired renal function through 38 pregnancies and compared creatinine clearance derived from a 24-hour urine collection with the Cockcroft–Gault eGFR during each trimester. While the study showed good correlation between this eGFR and creatinine clearance, I hesitate to recommend national usage based on a single study of 34 women. As recommended by the K/DOQI guidelines and commonly used by obstetricians, the accepted method for the determination of GFR in pregnancy is still the 24-hour urine collection with formal calculation of creatinine clearance.

Pregnancy can occur in women with all stages of renal impairment, including women on dialysis or after transplantation. Fertility is diminished and the risk of harm to the fetus is increased if a woman with renal impairment has a pre-pregnancy GFR of $<70 \text{ mL/min}/1.73\text{m}^2$.⁴ Given that there is an almost 50% increase in GFR between early pregnancy and delivery,⁴ it is possible that even if the MDRD-based eGFR accurately and precisely estimated GFR, reporting high eGFR simply as $>60 \text{ mL/min}$ could result in failure to detect renal impairment in some pregnant women.

While I strongly support the effort to improve our recognition of chronic kidney disease, I urge caution with regard to implementing a scheme in the specific population of pregnant women when this scheme has not been adequately studied. Perhaps a multi-centre cooperative study is in order.

1 The Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 2005; 183: 138-141.

2 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39 (2 Suppl 1): S1-S266.

3 Quadri K, Bernardini J, Greenberg A, et al. Assessment of renal function during pregnancy using a random urine protein to creatinine ratio and Cockcroft–Gault formula. *Am J Kidney Dis* 1994; 24: 416-420.

4 Davidson J, Bayliss C. Renal disease. In: de Swiet M, editor. Medical disorders in obstetric practice. 4th ed. Oxford: Blackwell Science Ltd, 2002. □

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TO THE EDITOR: The Australasian Creatinine Consensus Working Group has issued an important statement¹ that highlights the perils of relying on serum creatinine concentration alone to estimate kidney function. However, the suggestion that the recommended eGFR (estimated glomerular filtration rate) “is not appropriate for use . . . [in certain groups, such as] Aboriginal and Torres Strait Islander populations” and that “GFR should be measured directly” in such populations is poorly worded and clinically inappropriate.

The two most commonly used formulas for eGFR calculation (the Cockcroft–Gault and MDRD [Modification of Diet in Renal Disease] equations) are both derived from studies in US subjects, with a correction factor added for African-Americans.^{2,3} Concerns have recently been raised about other ethnic groups.⁴ As neither formula has been validated in any specific Australian majority or minority group, to recommend exclusion of Aboriginal and Torres Strait Islander populations without data is inappropriate.

In the Northern Territory, rates of kidney disease in Indigenous Australians are 20–30 times those in the white population. In addition, Indigenous Australians have limited access to basic health care, let alone “direct measurements of GFR”. We believe that, until data are available on the validity of the MDRD formula for specific minority groups, the best clinical care can be delivered by measuring the serum creatinine concentration and calculating eGFR (using the MDRD equation) in all Australians. We have been using this approach for over 2 years.

Therefore we suggest the following alternative to the Working Group’s recommendation:

Estimated GFR should be reported for all people aged ≥ 18 years, but cautious interpretation should be used in population groups with limited or no validation data.

- 1 Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 2005; 183: 138-141.
- 2 Cockcroft D, Gault MK. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31-41.
- 3 Levey AS, Bosch JP, Lewis JB, et al. 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: 461-470.
- 4 Zuo L, Ma Y-C, Zhou Y-H, et al. Application of GFR-estimating equations in Chinese patients with chronic kidney disease. *Am J Kidney Dis* 2005; 45: 463-472. □

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TO THE EDITOR: I read with interest the position statement¹ recommending that Australian laboratories use the recently published MDRD (Modification of Diet in Renal Disease) equation² to estimate glomerular filtration rate (GFR) and automatically report the estimated GFR (eGFR) when the value is less than 60 mL/min/1.73m².

Serum creatinine concentration provides an imperfect guide to renal function because it is affected by factors other than glomerular filtration. To improve the accuracy of the estimate of GFR, more than 40 equations and nomograms have been developed over the years. One of these, the MDRD equation, was found to give a better estimate than the most commonly used equation (the Cockcroft–Gault equation³) in a study that (it might be argued) favoured the MDRD method.² The abbreviated MDRD equation recommended in the position statement has only been published as an abstract.⁴

The position statement notes that “an uncorrected eGFR may be preferred for clinical use in some situations, such as drug dosing”, which requires the reported eGFR to be modified for body surface area (BSA). However, the formula quoted in the position statement is incorrect. The correct formula, published in 1916⁵ is:

$$BSA = W^{0.425} \times H^{0.725} \times 0.007184$$

This complicated equation requires data that are infrequently available, and it is arguable that performing this extra calculation may negate any benefit from the “improved” MDRD estimate. While the authors of the position statement do not recommend that reported eGFRs be used to calculate drug doses for patients with renal impairment, it is likely that they will be used for that purpose, without modification, by prescribers unaware of the limitations.

For patients requiring drug dosage reductions, it is doubtful whether the MDRD formulas give a more accurate eGFR than the Cockcroft–Gault equation, which has not only provided useful bedside estimates of GFR for decades, but has also been a valuable teaching tool. By incorporating age, sex and weight, the Cockcroft–Gault equation reminds us that these factors affect creatinine production and hence serum creatinine concentration. The same cannot be said for the MDRD formulas, which are complex, difficult to remember, and require a personal digital

assistant or similar device for doing the calculations.

In estimating the dose of renally cleared drugs, it has been observed that “what is essential for therapeutic decisions is knowing that a patient’s renal function is impaired and about to what extent, rather than the exact glomerular filtration rate”.⁶ Since estimates of renal function will never preclude drug concentration monitoring, modest improvements in accuracy of an estimated parameter are of limited benefit. I recommend the continued use of the Cockcroft–Gault equation for estimating doses of renally cleared drugs.

- 1 Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 2005; 183: 138-141.
- 2 Levey AS, Bosch JP, Lewis JB, et al. 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: 461-470.
- 3 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31-41.
- 4 Levey AS, Greene T, Kusek JW, et al. A simplified equation to predict glomerular filtration rate from serum creatinine [abstract]. *J Am Soc Nephrol* 2000; 11: A828.
- 5 DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 1916; 86:3-871.
- 6 Reidenberg MM. Kidney function and drug action. *N Engl J Med* 1985; 13: 816-817. □

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TO THE EDITOR: The publication of an Australasian position statement on reporting estimated glomerular filtration rates (eGFRs)¹ is welcome. It may, however, contain errors and unexplained assumptions.

Firstly, along with its US² and UK³ counterparts, the position statement recommends the use of the MDRD (Modification of Diet in Renal Disease) four-variable formula to derive eGFR from a patient’s serum creatinine level. Results obtained using this formula are more accurate than those from a patient’s calculated creatinine clearance rate. In accordance with the US guidelines, the Australasian position statement specifies that the total error in laboratories’ serum creatinine measurements should be less than $\pm 15\%$ if they are to meet overall reporting acceptability. It claims that results that lie within $\pm 15\%$ of results derived from the reference method procedure (isotope dilution mass spectrometry) also lie within $\pm 15\%$ of results based on applying the MDRD formula to CX3 analyser readings and thus “fulfil

the accuracy criterion". Australian physicians should be wary of this claim. Assays from which the MDRD formula was derived were reportedly performed on an older analyser than the CX3,⁴ with possibly even less accurate results. Serum creatinine results produced by a CX3 analyser are themselves about 16% positively biased compared with results calculated by the reference method.⁵ It is thus possible to be within 15% of a CX3 result and yet, at worst, be >30% shy of the "true" creatinine value assayed by the reference method. Laboratories should explain to clinician clients the limitations of their creatinine assays.

Secondly, the precision of an assay varies with the level of analyte being analysed — a nuance to be considered, but too technically complex to address further here. The position statement barely touches on this issue.

Thirdly, the position statement opts for 60 mL/min/1.73m² as the upper limit for reliable reporting of eGFR. It offers reasons why it takes this approach, but does not explain why the chosen level varies from US and UK reporting practices (both choose 90 mL/min/1.73m² as the cut-off point).

Finally, the UK guidelines sensibly changed the US terminology for racial derivation from "African-American" to "African-Caribbean" when indicating a need to adjust the eGFR reported. The Australasian position statement adopts the term "African-American". Australasian Africans are not African-Americans, nor do all Africans have similar physical stature to people whose ancestors lived in sub-Saharan west and central Africa and who became slaves in the United States or lived in English Caribbean colonies. More care will be needed in reporting here if clinicians are not to be needlessly confused.

1 Australasian Creatinine Consensus Working Group. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: a position statement. *Med J Aust* 2005; 183: 138-141.

2 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002; 39 (2 Suppl 1): S1-S266. Available at: http://www.kidney.org/professionals/kdoqi/guidelines_ckd/toc.htm (accessed Jul 2005).

3 Joint Specialty Committee on Renal Disease. Chronic kidney disease in adults: UK guidelines for identification, management and referral. June 2005. Available at: <http://www.renal.org/CKDguide/full/UKCKD-full.pdf> (accessed Jul 2005).

4 Levey AS, Bosch JP, Lewis JB, et al. 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: 461-470.

5 Miller WG, Myers GL, Ashwood ER, et al. Creatinine measurement: state of the art in accuracy and inter-laboratory harmonization. *Arch Pathol Lab Med* 2005; 129: 297-304. □

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IN REPLY: Jose and Lawton identify a concern about the wording in the position statement relating to one of the caveats on the use of estimated glomerular filtration rate (eGFR).

The intention of the Australasian Creatinine Consensus Working Group was to highlight that, in certain populations, the MDRD (Modification of Diet in Renal Disease) formula for calculating GFR has not been validated, and that, in such populations, caution should be exercised in applying the formula. This conservative approach was deemed appropriate, as significant population differences in muscle mass (such as have been documented between whites and African-Americans and between men and women) could lead to a formula correction factor being applied in these groups.

It was not the intention of the Working Group to deny the advantages of automatic reporting of eGFR to any section of the community. The sparse evidence that exists suggests that the amount of fat-free mass found in Indigenous Australians does not differ from that found in non-Indigenous Australians.¹ In retrospect, it may have been more appropriate for the position statement not to have singled out Indigenous Australians for special mention.

The real need is for the eGFR formula to be validated in Aboriginal and Torres Strait Islander populations so that a firm basis for its use can be established and a correction factor applied if that is found to be required. Until this evidence is available, it appears clinically appropriate for the eGFR to be calculated and used prudently in Indigenous Australians.

Jones is mistaken in stating the body surface area formula we quoted is incorrect. The formula is expressed with the correction factor to normal body size incorporated, and is correct in the context in which it was used. We agree with his recommendation to continue using the Cockcroft–Gault formula for estimating doses of drugs cleared by the kidney, at least until evidence for this purpose is accumulated using the MDRD formula.

Davey raises the possibility that significant errors may occur as a result of poor standardisation of serum creatinine assays. There is indeed room for improvement in routine assays for serum creatinine, but we believe, based on available data, that the current assays from most major suppliers are suitable for the

purpose. Further details on acceptable assays have been provided by the Working Group for all Australian laboratories.² Davey notes the presence of two reference standards for serum creatinine in the position statement: the CX3 method (which was used in the original MDRD article) and the international reference method (IRM). We believe that assays aligned with either of these standards meet the specifications, as the IRM gives lower results than the CX3 method and there are no current commercial assays giving results lower than the IRM. Thus, any current assays within 15% of the IRM are higher than the IRM and within 15% of the CX3 method. Furthermore, the claim of a positive bias of 16% for the current CX3 assay is taken at a single creatinine concentration that is below those that may be used for eGFR calculations. As this bias is absolute rather than proportional, it is not as marked at higher creatinine concentrations. Other studies do not support this degree of difference.

We agree that improvements in creatinine assay standardisation will be of benefit, and this issue is actively being pursued by working groups of the International Federation of Clinical Chemistry and Laboratory Medicine and the National Kidney Disease Education Program (NKDEP). Indeed, the attention given to serum creatinine assays as part of the deliberations of these groups is of benefit to any clinical assessment based on serum creatinine results.

The upper limit of reporting eGFR, recommended at 60 mL/min/1.73m², is in keeping with the position statement of the NKDEP in the United States,³ although not with the position of the Renal Association in the United Kingdom, which recommends reporting up to 90 mL/min/1.73m².⁴ At this stage, we believe that assay variability at lower creatinine concentrations and lack of validation of the MDRD formula at higher values for eGFR make 60 mL/min/1.73m² a suitable starting point. We hope that, with improvements in both these factors, a higher limit may be acceptable.

1 Rutishauser IH. Body composition in Aboriginal Australians. *Asia Pacific J Clin Nutr* 1995; 4: 73-76.

2 Jones G, for the Working Party on routine reporting of eGFR. Routine reporting of eGFR. Laboratory implementation guidelines. Available at: <http://www.aacb.asn.au/pubs/eGFR%20Laboratory%20Guidelines.PDF> (accessed Nov 2005).

3 National Kidney Disease Education Program. Resources: suggestions for laboratories. Available at: http://www.nkdep.nih.gov/resources/laboratory_reporting.htm (accessed Nov 2005).

4 Joint Specialty Committee on Renal Disease. Chronic kidney disease in adults: UK guidelines for identification, management and referral. June 2005. Available at: <http://www.renal.org/CKDguide/full/UKCKD-full.pdf> (accessed Jun 2005). □