Using the modification of diet in renal disease (MDRD) and Cockcroft and Gault equations to estimate glomerular filtration rate (GFR) in older people

SIR—Kidney function is typically assessed by measuring the glomerular filtration rate (GFR) and the internationally accepted classification of chronic kidney disease (CKD) is largely predicated by GFR [1]. Part 2 of the Renal National Service Framework [2] addressed prevention and early detection of CKD and recommended that laboratories report a formula-based estimation of GFR (estimated GFR, eGFR) on requests received for serum creatinine measurement in adults. In April 2006 the Department of Health introduced universal eGFR reporting in England [3] using the modification of diet in renal disease (MDRD) study equation [4–6]. Simultaneously, the General Medical Services contract’s Quality and Outcomes Framework introduced a register of people in primary care with CKD. Other healthcare organisations interested in kidney disease have made similar recommendations and consensus guidelines designed to improve the management of patients with CKD have been promulgated [7, 8].

Epidemiological studies using the standardised MDRD equation suggest an overall non-institutionalised population burden of CKD of approximately 11% [9]. However, prevalence increases dramatically in older people, where, in excess of 25% of the population over the age of 70 years are thought to have a GFR consistent with stage 3 CKD or worse (i.e. GFR <60 ml/min/1.73 m², [9–11]).

The MDRD equation was not initially validated in older people, the age group amongst whom most CKD would appear to reside. There has only been limited subsequent evaluation in this population and this may lead to concerns that the MDRD equation does not accurately reflect true GFR in older people. Our original study addressed this issue [12], but the method that we used to measure creatinine was different from that used in the original MDRD study. The critical importance of creatinine assay standardisation when using the MDRD equation to estimate GFR is now widely appreciated [13]. Grossly different estimates of GFR can be obtained by using creatinine methods that are positively or negatively biased compared to the original MDRD creatinine assay (Beckman Astra CX3 method), which was undertaken in the Cleveland Clinic Foundation (CCF) laboratory. We have subsequently been able to standardise our own creatinine assay to that of the CCF [14]. Here we re-analyse our earlier data using standardised creatinine results and report the performance of the MDRD equation in a group of older people. For comparison, the performance of the Cockcroft and Gault equation [15] is also reported.

Methods

The clinical, prescribed drug and biochemical characteristics of our cohort have been reported previously [12]. Of the 52 patients originally recruited to the study, 46 had residual...
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serum enabling traceability to the CCF creatinine assay to be established. Patients were fairly typical of the mix encountered in a healthcare of the older person outpatient setting. All were Caucasian and there were 23 males and 23 females. The mean (±SD) age was 80 (±4.9) years (range 69–92 years). GFR was measured using a $^{51}$Cr EDTA technique and results were corrected to a body surface area (BSA) of 1.73 m$^2$ [16]. Mean (±SD) $^{51}$Cr EDTA GFR was 54.7 (±17.0) ml/min/1.73 m$^2$ (range 23.8–100.2). All subjects gave informed consent and the study had full ethical approval.

Serum creatinine was measured using an uncompensated Jaffe assay (Roche Diagnostics plc, Lewes, Sussex, UK) as described elsewhere [17]. The uncompensated Jaffe creatinine results were converted to compensated Jaffe creatinine results using the known relationship between the two assays [17]:

$$\text{creatinine}_{\text{compensated}} = (1.098 \times \text{creatinine}_{\text{uncompensated}}) - 19.7.$$  

The compensated Jaffe results were then converted into CCF equivalent data using the known relationship between the assays [14]:

$$\text{creatinine}_{\text{Beckman}} = (\text{creatinine}_{\text{compensated}} + 17.5)/0.9566.$$  

GFR was estimated by substituting the CCF equivalent creatinine data (µmol/l) into both the MDRD and Cockcroft and Gault equations:

MDRD eGFR (ml/min/1.73 m$^2$) = $186 \times (\text{creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times 0.742$ (if the subject is female)

Cockcroft and Gault eGFR (ml/min) = $(140 - \text{age} \text{ (years)}) \times \text{weight (kg)}/(0.814 \times \text{creatinine}) \times 0.85$ (if the subject is female)

The Cockcroft and Gault estimate was corrected to a BSA of 1.73 m$^2$ [16]. Normality of the distribution of the GFR estimates was tested using Kolmogorov–Smirnov test. The two GFR estimates were compared against the $^{51}$Cr EDTA GFR using least squares linear regression and bias plot analysis. Differences from $^{51}$Cr EDTA GFR were tested using the paired $t$-test.

Results

None of the GFR datasets demonstrated significant deviation from a normal distribution ($P>0.15$). eGFR using the MDRD equation showed no significant bias ($P>0.05$) and reasonable precision compared to $^{51}$Cr EDTA GFR measurement. There was no evidence of a relationship between bias and level of GFR (Table 1, Figure 1). The Cockcroft and Gault equation significantly underestimated GFR in older people ($P<0.0001$) and showed poor precision of the estimate. The Cockcroft and Gault estimate was increasingly negatively biased at higher levels of GFR [difference (ml/min/1.73 m$^2$) = $(-0.4066 \times \text{EDTA}_{GFR}) + 11.1$, $R^2 = 0.52$, $P<0.0001$, Figure 1], but there was no relationship between bias and weight.

Discussion

The MDRD equation, which estimates GFR adjusted for BSA, was developed using data from 1,628 patients with CKD. The mean age was 50.6 ± 12.7 y and mean $^{125}$I-iothalamate GFR 39.8 ± 21.2 ml/min/1.73 m$^2$ [4]. A simplified (4-variable) version of the equation has subsequently been published [5, 6]. In the MDRD study population, 91% of GFR estimates were within 30% of the measured values and the equation explained 90.3% of variation in GFR.

Although an equation developed in one population may be appropriate for use in that population, its use in other populations needs to be tested. A number of such studies in a variety of clinical settings have been conducted (reviewed in [18]). Generally, the MDRD equation has performed slightly better, and offers practical
advantages, over other GFR estimating equations. However, there remains a dearth of evidence supporting its use in older people. Van den Noortgate et al. [19] studied 48 patients with a mean (±SD) age of 84 (±6) years. Serum creatinine was measured with a method known to be negatively biased compared to the CCF method [14]: consequently the MDRD formula overestimated GFR (mean bias 10.5 ml/min/1.73 m²) compared to ⁵¹Cr EDTA GFR. In the largest published study so far of 2,095 adult Europeans predominantly being investigated for CKD, Froissart et al. [20], using a creatinine method aligned to the CCF assay, undertook a sub-analysis in patients >65 years old and with GFR <60 ml/min/1.73 m². Performance of the MDRD formula was generally comparable to that amongst younger individuals, tending to give a slightly negatively biased estimate of GFR (mean bias −1.0 ml/min/1.73 m²). However, only 57 subjects were aged 80 years or older (M Froissart, personal communication).

We originally reported a mean positive bias of 6.3 ml/min/1.73 m² compared to ⁵¹Cr EDTA GFR for the MDRD equation, and a negative bias of 5.2 ml/min/1.73 m² for the Cockcroft and Gault equation: precision was marginally better for the Cockcroft and Gault equation [12]. In the present reanalysis of this data, eGFR using the MDRD equation showed no significant bias and reasonable precision compared to ⁵¹Cr EDTA GFR. In contrast, the Cockcroft and Gault equation significantly underestimated GFR (mean bias −11.2 ml/min/1.73 m²) and was imprecise (Table 1). The difference from our original report is readily explicable on the basis of the known assay characteristics. The Beckman Astra CX3 assay used in the CCF laboratory is known to have a positive bias compared to many creatinine assays and also compared to ‘zero-biased’ enzymatic and isotope-dilution mass spectrometry methods [21]. Therefore adjusting our earlier creatinine results to resemble this assay has further increased the previously observed negative bias of the Cockcroft and Gault equation whilst at the same time minimising the previously observed positive bias of the MDRD equation.

As is now appreciated, creatinine-based GFR estimating equations are only valid when used with the creatinine assays with which they were derived. It is therefore unreasonable to imply criticism of the Cockcroft and Gault equation on the basis of this data, and the results are merely shown for comparison. That the Cockcroft and Gault equation yields lower estimates of GFR than the MDRD equation in older people is consistent with other reports, including a recent large-scale study by Pedone et al. [22], although no reference GFR procedure was available to these investigators. What can be concluded from our results, however, is that when the MDRD equation is used in this population with adjustment of the creatinine assay to resemble that with which it was derived, performance is reasonable. As such, our data agrees with that of Froissart et al. [20].

With an ageing population and increasingly complex polypharmacy, the accurate estimation of GFR and detection and management of renal impairment is clearly an important issue in older people [23]. Currently, the MDRD equation is being applied to this population amongst whom limited evaluation has been undertaken and the relationship between age and GFR is being extended beyond that in which it was established. However, although we have only studied a small number of patients, our data provides some evidence that the MDRD equation works reasonably in this population. This needs confirmation in larger studies.

**Key points**

- CKD is prevalent amongst older people.
- Currently used (MDRD) GFR estimating equations have not been well validated in this population.
- The data presented in this paper does not suggest that the MDRD equation is inaccurate when used in older people.

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### Table 1. Comparison of the Cockcroft and Gault and modification of diet in renal disease (MDRD) formulae on estimates of glomerular filtration rate (GFR) in 46 older people

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<th>Regression analysis</th>
<th>Difference plot analysis</th>
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<td>Mean, SD, Intercept</td>
<td>Limits of agreement (95% CI), ml/min/1.73 m²</td>
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<td></td>
<td>ml/min/1.73 m²</td>
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<td>R², Slope</td>
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<td>GFR (⁵¹Cr EDTA)</td>
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<tr>
<td>Cockcroft and Gault</td>
<td>43.5, 12.1, 0.69</td>
<td>−11.2 (−14.1 to −8.4)</td>
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<tr>
<td>MDRD</td>
<td>52.7, 16.2, 0.78</td>
<td>−2.0 (−4.4 to 0.4)</td>
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</tbody>
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* Significantly (P<0.01) different from zero.

* Significantly (P<0.0001) different from ⁵¹Cr EDTA clearance.

SD, standard deviation; CI, confidence interval.

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References


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Conflict of interest

None

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