GFR prediction using the MDRD and Cockcroft and Gault equations in patients with end-stage renal disease

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Abstract
Background. Although prediction equations are recommended to determine GFR and creatinine clearance (CrCl), neither the MDRD equations nor the Cockcroft and Gault formula have been validated for the low levels of GFR present in end-stage renal disease (ESRD). The accuracy of the MDRD equations and the Cockcroft and Gault formula in predicting GFR and CrCl, respectively, was examined in patients with ESRD and its relationship to the basal GFR and two markers of malnutrition, urinary creatinine and body fat determined.

Methods. Inulin clearance (C\textsubscript{in}) was measured in 26 non-diabetic patients with ESRD and the 24 h CrCl determined. GFR was predicted using three equations derived from the MDRD study population containing four to six variables. Both CrCl and GFR were predicted from the Cockcroft and Gault formula. Estimates of bias and precision were obtained and Bland and Altman analysis performed. Body fat was measured by DEXA scan.

Results. The predicted GFR (MDRD) was 10% lower than C\textsubscript{in} (8.83±0.71 ml/min/1.73 m\textsuperscript{2}) with all three MDRD equations, showing a similar degree of precision and bias. C\textsubscript{in} gave a negative correlation with the difference between the predicted GFR (MDRD) and the measured GFR. The predicted GFR (MDRD) underestimated GFR when C\textsubscript{in} > 8 ml/min/1.73 m\textsuperscript{2} but overestimated GFR when C\textsubscript{in} < 8 ml/min/1.73 m\textsuperscript{2}. The Cockcroft and Gault formula underestimated CrCl by 14% and overestimated C\textsubscript{in} by 35%. C\textsubscript{in} gave a negative correlation with the difference between the predicted GFR (Cockcroft and Gault) and measured GFR, overestimating GFR when C\textsubscript{in} < 13 ml/min/1.73 m\textsuperscript{2}. The overestimation of GFR by the MDRD equation was not associated with urinary creatinine excretion. However, both Cockcroft and Gault and the MDRD predictions showed a positive, but weak, correlation with body fat.

Conclusion. The MDRD equations were more accurate in predicting the group mean GFR in patients with ESRD than the Cockcroft and Gault formula. However, the predicted GFR using either formula was related to the basal GFR and percentage body fat.

Keywords: chronic kidney disease; end-stage renal disease; Cockcroft and Gault; glomerular filtration rate; inulin clearance; Modification of Diet in Renal Disease study

Introduction
The National Kidney Foundation Dialysis Outcome Quality Initiative (K/DOQI) [1] and European Best Practise Guidelines [2] recommend the use of prediction equations to estimate the GFR from serum creatinine. In adults, the most commonly used formulae are those derived from the Modification of Diet in Renal Disease (MDRD) study population [3] and that by Cockcroft and Gault [4]. The MDRD equations were derived from patients with varying degrees of renal impairment employing a stepwise regression technique, with GFR measured from the renal clearance of \textsuperscript{[125I]}iothalamate [3]. In its original form, the MDRD formula (equation 7) used six variables (serum creatinine, albumin and urea nitrogen, gender, age and ethnicity), although two simpler equations requiring either five variables (excluding serum albumin) or four variables (excluding serum albumin and urea nitrogen) were proposed to offer a similar performance [5]. The Cockcroft and Gault formula, in marked contrast, was constructed from hospitalized patients to predict creatinine clearance from the serum creatinine in the absence of urine collection [4].

Due to the demographically sensitive nature of creatinine measurement, GFR prediction equations cannot always be applied to individual patient
groups [6]. Neither the MDRD nor Cockcroft and Gault formulae were suitable to predict GFR in patients without kidney disease [7]. In patients with CKD but a normal serum creatinine, the Cockcroft and Gault formula was found to be more accurate than the MDRD equation [8]. In scleroderma patients with renal impairment, GFR predicted using the MDRD equation showed the better correlation with 51Cr EDTA clearance than the Cockcroft and Gault formula [9]. The original paper on the MDRD prediction equations by Levey et al. [3] carried a note added in proof, validating the formula in patients with end-stage renal disease (ESRD) at the initiation of dialysis. Data published in abstract form showed the full MDRD equation to overestimate [125I] iothalamate clearance by 5% compared with Cockcroft and Gault where the overestimate was 16% [10]. The present study was undertaken to compare the accuracy of the GFR predicted using either the MDRD equations or the Cockcroft and Gault formula in patients with ESRD. However, equations derived from the MDRD study population with mainly mild to moderate CKD may not necessarily be appropriate for patients with ESRD where important changes in body composition may occur due to fluid retention and malnutrition. The predicted GFR was related to the basal GFR, measured from the renal clearance of inulin (C<sub>in</sub>), together with two markers of malnutrition, urinary creatinine and body fat determined by DEXA scan.

Subjects and methods

Patients

Patients were recruited into this study from a population (n = 550) with chronic kidney disease (serum creatinine >200 μmol/l, male n = 385, female n = 165, non-Caucasian n = 27) under follow-up at the Sheffield Kidney Institute, Northern General Hospital, Sheffield, UK. Inclusion criteria into the study included serum creatinine >400 μmol/l, 18–70 years old and biochemical/clinical features of progressive renal impairment over the last 12 months. Exclusion criteria included diabetes mellitus, pregnancy and lactating mothers. Twenty-seven patients were ultimately recruited (26 Caucasian and 1 Asian). However, the Asian subject was excluded since any correction necessary for demographic differences in the Asian population is, at present, unknown. Three days prior to GFR measurement, a 24 h urine sample was collected to calculate creatinine clearance. Body weight and height were measured to calculate body surface area [11]. The body mass index (BMI) was calculated as body weight (kg)/body height (m)<sup>2</sup>. Serum samples were taken for the analysis of creatinine, albumin and urea nitrogen.

GFR was measured following an overnight fast. Basal blood and urine samples were obtained and each patient received 10 ml Inutest (Fresenius Pharma, Linz, Austria) by slow intravenous injection. Inutest contains 25% inulin, in the form of its water-soluble, branched chain analogue sinistrin. Accurately timed blood samples (5 ml) were obtained after 2, 3, 4 and 5 h. At 2 h patients were asked to completely empty their bladder, complete urine collections were obtained at 3, 4 and 5 h and the urine volume recorded. Plasma and urine samples were assayed as described below and C<sub>in</sub> calculated for each 1 h collection period. The average of three 1 h measurements of C<sub>in</sub> was obtained and standardized to a body surface area of 1.73 m<sup>2</sup>

Body composition was measured using Dual-Energy X-ray Absorptiometry (DEXA) scan (Lunar DPX; GE Medical Systems, WI, USA) within 7 days of the renal clearance measurement.

Assays

Creatinine, urea and albumin were assayed in serum using an autoanalyser (Synchro LX 20; Beckman Coulter, High Wycombe, UK) by the Department of Clinical Chemistry, Northern General Hospital, Sheffield. The coefficient of variation for the assay of creatinine was 4.5%. Inulin was assayed in plasma and urine by a double enzyme method adapted for a plate reader (Multiskan Ascent, Labsystems) [12]. Briefly, inulin was metabolized to fructose by inulinase (Fructozyme, Novo-Nordisk, Denmark) and the fructose generated was further metabolized to sorbitol by sorbitol dehydrogenase (Roche Diagnostics, UK). Full hydrolysis was achieved by the conditions employed. The fructose content was quantified from the utilization of an exogenous co-factor NADPH, read at 340 nm. Unless otherwise stated, all reagents were obtained from Sigma (Poole, UK).

Formula calculations

GFR was estimated using the formulae identified in Table 1. The full MDRD equation containing six variables was equation 7 described by Levey et al. [3]. The MDRD equations containing four and five variables were described in abstract by Levey et al. [5]. The Cockcroft and Gault formula was used unadjusted for body surface area unless indicated. As all subjects were of Caucasian origin, ethnicity was not a variable in this study.

Statistics

The accuracy of each prediction equation was described from the percentage of predicted GFR values falling within

| Table 1. Prediction equations from the MDRD study population and by Cockroft and Gault (C&G) to calculate the GFR and creatinine clearance, respectively |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| MDRD (six variables) [3]        | 170 × SCr<sup>−0.999</sup> × age<sup>−0.176</sup> × SUN<sup>−0.170</sup> × SAlb<sup>0.318</sup> (0.762 female) × (1.180 black) |
| MDRD (five variables) [5]       | 270 × SCr<sup>−1.007</sup> × age<sup>−0.180</sup> × SUN<sup>−0.166</sup> × (0.755, if female) × (1.178, if black) |
| MDRD (four variables) [5]       | 186.3 × SCr<sup>−1.154</sup> × age<sup>−0.203</sup> × (0.742 female) × (1.212 black) |
| C&G [4]                         | [((140 – age) × weight) [(2 × SCr(mg/dl))] × (0.85 if female)] |

SCr, serum creatinine (mg/dl); SUN, serum urea nitrogen (mg/dl); SAlb, serum albumin (g/dl).
30 or 50% (above or below) the measured GFR. A high level of accuracy requires both low bias and high precision.

Bias is a measure of the systemic deviation of the predicted from the measured GFR calculated as the mean prediction error (ME):

$$ ME = \frac{\sum PE_i}{N} $$

where $PE_i$ = predicted GFR – measured GFR and $N$ = number of patients.

The precision and bias of GFR prediction equations is shown graphically using Bland and Altman analysis [13]. The difference between the predicted and measured GFR was plotted against the average of the predicted and measured GFR as a measure of the concordance between the two techniques. The limits of agreement are given by the mean ± 2 SD.

A test of correlation was performed by Spearman’s coefficient using the SPSS 12 statistics package. A $P$-value of <0.05 was considered to be significant.

## Results

The anthropometric and biochemical characteristics of patients with ESRD ($n = 26$) are shown in Table 2. The mean value of $C_{in}$ was $8.83 \, \text{ml/min/1.73 m}^2$, with 73% of patients having a measured GFR of <10.5 ml/min/1.73 m$^2$. Group mean values for the GFR predicted from the MDRD equations are compared with $C_{in}$ in Table 3. For each of the three MDRD equations, the mean predicted GFR was lower than the measured inulin clearance by ~10%, although the difference did not reach statistical significance. Nearly 70% of patients were within 30% and nearly 90% within 50% of the measured GFR. All MDRD equations gave a significantly positive, but weak, linear correlation with $C_{in}$ (Figure 1, left-hand diagrams) together with a highly significant linear correlation with each other ($r = 0.98, P < 0.00001$). Bland and Altman analysis (Figure 1, right-hand diagrams) plots the difference against the mean of the predicted and measured GFR. Precision is shown by the distribution of data with limits of mean ± 2 SD represented by long dotted lines. Bias is shown by the systematic deviation of the mean (dotted line) from zero (solid line). All MDRD equations showed a similar degree of precision and bias to each other.

The group mean creatinine clearance predicted from the Cockcroft and Gault formula was 12.17 ml/min, overestimating the measured creatinine clearance by 14% ($P < 0.05$). In clinical practise, the Cockcroft and Gault formula has also been used to predict GFR. The GFR predicted using the Cockcroft and Gault formula overestimated $C_{in}$ by 35% with <50% of patients within 30% and only 60% of patients within 50% of the measured GFR. The Cockcroft and Gault formula showed a similar degree of precision to the MDRD equations but with a considerably greater bias.

### Baseline GFR

The relationship between basal inulin clearance and the ability of either the MDRD six variable equation or the Cockcroft and Gault formula to predict the GFR in patients with ESRD is shown in Figure 2. The difference between the predicted GFR (MDRD six variable) and the measured GFR gave a negative linear regression with $C_{in}$ (Figure 2A). The linear line of best fit intercepted zero on the x-axis, i.e. when the predicted equalled the measured GFR, at a $C_{in}$ of 8 ml/min/1.73 m$^2$. Therefore, when GFR <8 ml/min/1.73 m$^2$, the MDRD six variable equation overestimated $C_{in}$ but when GFR of >8 ml/min/1.73 m$^2$, the MDRD six variable equation underestimated $C_{in}$. The difference between the predicted GFR (Cockcroft and Gault) and the measured GFR also gave a negative linear regression with $C_{in}$ (Figure 2B). However, since the linear line of best fit intercepted zero on the x-axis at a $C_{in}$ of 13 ml/min/1.73 m$^2$, the GFR predicted using the Cockcroft and Gault formula mainly overestimated $C_{in}$ in our ESRD patient cohort.

### Urinary creatinine

The relationship between urinary creatinine excretion and the difference between the predicted GFR (MDRD six variable) and renal function measured from either 24 h CrCl or $C_{in}$ is shown in Figure 3A and B. Urinary

## Table 2. Anthropometric and biochemical characteristics of patients with ESRD

| Number | 26 (14 male and 12 female) |
| Age (years) | 53 ± 13 (30–70) |
| Body weight (kg) | 77 ± 16 (47–105) |
| BMI | 26.6 ± 4.3 (20.7–34.8) |
| Body surface area (m$^2$) | 1.87 ± 0.23 (1.4–2.3) |
| Body fat (%) | 33.0 ± 10.0 (11.3–52.4) |
| Serum creatinine (mg/dl) | 7.48 ± 1.82 (4.86–10.31) |
| Serum urea nitrogen (mg/dl) | 78.8 ± 19.4 (30.5–119.1) |
| Serum albumin (g/dl) | 3.93 ± 0.49 (3–5) |
| Urinary flow rate (ml/h) | 133 ± 49 (57–229) |
| Inulin clearance (ml/min/1.73 m$^2$) | 8.83 ± 3.62 (2.21–18.85) |
| Creatinine clearance (ml/min) | 10.56 ± 4.29 (5.11–23.33) |

All the data expressed as mean ± SD (minimum–maximum).

## Table 3. The accuracy, precision and bias of equations from MDRD study population (ml/min/1.73 m$^2$) and Cockcroft and Gault (C&G) (ml/min) to predict the GFR in patients with ESRD

<table>
<thead>
<tr>
<th>Prediction equation</th>
<th>GFR (mean ± SEM)</th>
<th>Accuracy</th>
<th>Precision</th>
<th>Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>30%</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>MDRD (six variable)</td>
<td>8.04 ± 0.54</td>
<td>69.23</td>
<td>88.46</td>
<td>0.49</td>
</tr>
<tr>
<td>MDRD (five variable)</td>
<td>8.02 ± 0.52</td>
<td>69.23</td>
<td>88.46</td>
<td>0.46</td>
</tr>
<tr>
<td>MDRD (four variable)</td>
<td>7.81 ± 0.52</td>
<td>69.23</td>
<td>88.46</td>
<td>0.53</td>
</tr>
<tr>
<td>C&amp;G</td>
<td>12.17 ± 0.82</td>
<td>46.15</td>
<td>57.69</td>
<td>0.46</td>
</tr>
</tbody>
</table>
creatinine excretion (range 0.6–1.5 g/day) showed a significant negative linear correlation with the difference between the predicted GFR (MDRD) and CrCl but not when renal function was measured from inulin clearance.

Body fat

Our ESRD patient cohort had a mean body fat of 33% (±10) measured by DEXA scan (Table 2). The ratio between the GFR predicted by either the MDRD six variable equation (Figure 4A) or the Cockcroft and Gault formula (Figure 4B) and Cin showed a weak, positive linear correlation with the percentage of body fat. Both the formula to calculate body surface area and the Cockcroft and Gault formula contain the unit of body weight, which might contribute to the relationship with body fat. The use of a ratio rather than a subtraction method allowed measurements of BSA in both predicted and measured GFRs to cancel each other out. In addition, there was no correlation between body fat and body weight ($P = 0.29$) in this patient group.

Discussion

The GFR shows an important association with the appearance of uraemic symptoms in patients with ESRD [14]. The MDRD equations were used by the US
Renal Data System (USRDS) to predict the GFR at the initiation of dialysis where, for some 90,000 patients between 1995–1997, 86% had a predicted GFR of <8 ml/min [15]. Evidence that equations derived from the whole MDRD study population could be used to predict the GFR in ESRD was originally provided by data from the 88 out of 1647 patients who required renal replacement therapy during the study. The mean predicted GFR of this subgroup (9.6 ml/min/1.73 m²) exceeded the measured GFR (9.1 ml/min/1.73 m²) by only 5% [10]. In the present study the mean predicted GFR, obtained from a non-diabetic Caucasian ESRD population (8.04 ml/min/1.73 m²), did not significantly differ from C\textsubscript{in} (8.83 ml/min/1.73 m²). All three MDRD equations gave a similar level of precision and bias, indicating little advantage in ESRD to the additional measurements of serum albumin and urea nitrogen present in the full six variable MDRD equation. However, regression analysis showed a significant negative correlation for the difference between the predicted GFR (MDRD) and measured GFR against inulin clearance. When C\textsubscript{in} was <8 ml/min/1.73 m², the MDRD equation overestimated GFR but when C\textsubscript{in} was >8 ml/min/1.73 m², the MDRD equation underestimated GFR. As GFR declines in ESRD, the MDRD predicted GFR would tend to stabilize giving a false impression about disease progression, maybe even resulting in late initiation of dialysis. The MDRD equations would therefore appear to be less reliable predictors of GFR in ESRD than initially suggested [10].
In ESRD, the six variable MDRD equation has recently been shown to overestimate creatinine clearance at low values (mean 5.8 ml/min) but to underestimate creatinine clearance at higher values (mean 11.3 ml/min) using patients from the USRDS dialysis morbidity and mortality study II population [16]. Urinary creatinine excretion, a marker of creatinine production, gave a negative linear correlation with the difference between the predicted GFR (MDRD) and CrCl. Differences were attributed to the influence of malnutrition on urinary creatinine production, a measurement not factored into the MDRD equation. In the present ESRD study, a similar negative correlation between urinary creatinine excretion and the difference between the predicted GFR (MDRD) and CrCl could be demonstrated. However, no correlation was observed when inulin clearance rather than CrCl was employed. In addition, the overestimation of CrCl by the MDRD equation was observed in our study even though urinary creatinine excretion did not fall below 0.6 g/day; the level below which overestimation attributed to malnutrition was suggested to occur. Therefore, our data do not support the concept that the accuracy of the MDRD equation in predicting the GFR is a function of creatinine production [16]. We believe the basal GFR to be more relevant. It should also be remembered that in ESRD, urinary creatinine may be a poor measure of creatinine production since up to 70% of creatinine can be excreted extrarenally [17]. In fact, it would seem unlikely for the relationship between predicted (MDRD) and measured GFRs to be explained by a single factor. Since in the MDRD study population the mean GFR was 40 ml/min/1.73 m², it may simply be that the MDRD equations were not designed to fit the very low levels of GFR present in patients with ESRD.

The MDRD study used the renal clearance of [125I] iothalamate to assess the GFR. The use of inulin to measure the low levels of GFR for patients with ESRD in the present study may have been an important choice. In patients with chronic renal insufficiency [125I] iothalamate clearance has been reported to overestimate inulin clearance by 12% [18] and some animal evidence has been published for the tubular uptake and secretion of contrast media, which may be important at low levels of GFR [16]. Inulin clearance is the gold standard for the measurement of GFR and inulin clearances were performed using Inutest, a commercial injection containing inulin in the form of a branched chain rather than a straight chain fructose polymer. The branched chain structure produces a more water soluble injection although stronger acidic conditions were required on analysis for complete hydrolysis to fructose.

At present, K/DOQI guidelines suggest the Cockcroft and Gault formula should be used, as in clinical practise, in its unadjusted form. The Cockcroft and Gault formula was devised to predict creatinine clearance rather than the GFR [1]. In ESRD, the Cockcroft and Gault formula overestimated the 24 h creatinine clearance by a mean of 14% and overestimated inulin clearance by 35%, with only 60% of patients being within 50% of the measured GFR. The overestimation of GFR by the Cockcroft and Gault formula consists of at least three elements including (i) overestimation of creatinine clearance, (ii) overestimation by creatinine clearance of the GFR and (iii) lack of adjustment to standard body surface area. Creatinine clearance itself is known to overestimate GFR through tubular creatinine secretion. The decrease in GFR seen with renal progression is associated with an increase in the CrCl/GFR ratio,
an effect prevented by cimetidine, an inhibitor of renal tubular creatinine secretion [19]. In the MDRD study population, the predicted CrCl from the Cockcroft and Gault formula was adjusted to a standard body surface area but overestimated GFR by some 16%. An additional multiplier of 0.84 was employed to assess the GFR in patients with CKD [3]. Standardization of our creatinine measurements with that of a laboratory within the MDRD study to reduce systematic bias could have been considered, although this is of less relevance to ESRD patients where the serum creatinine is high [6]. However, in our ESRD population, the overestimate of GFR by the Cockcroft and Gault formula showed a negative correlation with C\text{cr}\text{in}, increasing as the GFR declined from 18 ml/min/1.73 m\text{2}. In ESRD, therefore, the GFR predicted from the Cockcroft and Gault formula cannot be simply adjusted using a factor for systematic deviation.

One factor contributing to the poor performance of both the MDRD equations and the Cockcroft and Gault formula to predict GFR in ESRD may have been obesity. The Cockcroft and Gault formula has previously been shown to produce large overestimates of creatinine clearance in obese patients with normal renal function and a formula was developed to calculate creatinine clearance in obese patients by assessing the fat-free body mass [20]. Body fat, determined from DEXA scans, ranged from 11.3 to 52.3%, with a mean BMI of 26.6 ± 4.3 kg/m\text{2}. The body fat showed a significantly positive, albeit weak, linear correlation with the ratio between the predicted GFR and C\text{cr}\text{in}. We do, however, acknowledge that the sample size for this study is small and that two of the data points are outliers that lie greater than two standard deviations from the population mean. A similar positive but weak linear correlation was also apparent with body fat using the MDRD six formula. Since both the Cockcroft and Gault formula and the body surface area use body weight in their calculation, the relationship could have been an artefact linking body weight to body fat. However in our study, no positive correlation between body weight and body fat was apparent.

Prediction equations need to be validated for the population in which they are to be used. Limitations of the present study included the small sample size which resulted in correlations which although statistically significant had low r values. The study was also undertaken in a non-diabetic Caucasian population so one might question its applicability to other ethnic groups with, for example, diabetic kidney disease. Like all cross-sectional studies, it also has the problem of its longitudinal application to the treatment of individual patients.

In conclusion, the MDRD equations were more accurate than the Cockcroft and Gault formula in predicting the group mean GFR in patients with ESRD. The results of the present study cast doubt on the use of GFR prediction equations in individual subjects where the accuracy of the GFR prediction was related to the basal GFR and body fat, but not to urinary creatinine excretion. A more accurate approach to GFR prediction might include local demographic factors, nutrition, body composition and peculiarities of patient co-morbidity through the use of neural networks.

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References


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