Modified diet in renal disease method overestimates renal function in selected elderly patients*

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Abstract

Background: the Modification of Diet in Renal Disease (MDRD) method of renal function estimation has not been extensively assessed in elderly patients. We needed to assess which renal function estimate was most suited for drug dose estimation in our population.

Method: we compared MDRD with an optimised version of the Cockcroft–Gault (CGopt) method in a hospital population, using gentamicin clearance as a baseline.

Results: MDRD overestimated gentamicin clearance by 29% (P < 0.001, n = 68), while CGopt underestimated by 10% (P < 0.01). Overestimation by MDRD increased with increasing age. This was 12%, 26% and 69% in age groups <65, 65–80 and >80 years respectively (P < 0.001). CGopt underestimated renal function by −5%, −16% and −4% respectively (P = NS). Bias and precision of renal function estimations for the three age groups were less for CGopt than for MDRD. Age significantly influenced MDRD overestimation in this population (P = 0.037).

Conclusion: MDRD overestimated renal function as age increased. While CGopt underestimated renal function, this was of a smaller magnitude, consistent across age, and thus better suited for dose calculation, especially in the elderly. Larger-scale studies using gold standard markers of renal function estimation are urgently needed to determine the accuracy of MDRD in elderly hospitalised patients.

Keywords: elderly, creatinine, gentamicin, drug dosing

Introduction

The National Kidney Foundation recommends estimation of renal function using equations based on serum creatinine values, suggesting two commonly used approaches. The first is the well-known Cockcroft–Gault (CG) equation, which provides an estimate of creatinine clearance (CrCl) [1]. The second is the Modification of Diet in Renal Disease (MDRD) study, which provides an estimation of glomerular filtration rate (GFR) [2]. This latter equation was developed in a relatively young population (mean age 51 ± 13 years) of chronic kidney disease (CKD) patients, with a view to staging kidney disease, and has subsequently been modified to the ‘abbreviated’ version commonly used today [3]. Comparative data indicate that the MDRD approach is more accurate than the CG equation in this population [2]. In a young, renally healthy population however (mean age 41 years), MDRD was shown to underestimate GFR by 29% [4]. In a population of older patients with chronic renal insufficiency (age range 69–92), MDRD overestimated renal function by 12%, and did not improve renal function estimation compared to the CG equation [5].

Historically, published data examining the accuracy of the CG approach have utilised the patient’s actual body weight. An optimised version of the CG equation (CGopt) has been developed that enables a more accurate estimation of renal function [6]. This involves two changes from the traditional CG approach. The first is use of the lesser of actual body weight or ideal weight [50 + 0.9 × (height in cm − 152) for males, 45.5 + 0.9 × (height in cm − 152) for females]. It
is known that without adjustment for obesity, CG markedly overestimates renal function [7]. The second alteration is the capping of serum creatinine at a minimum of 60 µmol/l (0.68 mg/dl). The use of values less than this leads to gross renal function overestimates. Low serum creatinine concentrations can be present in elderly patients due to a decreased muscle mass. Both these adaptations are important for elderly inpatient populations in order to obtain the best renal function estimation, which is of critical importance for dosing of key renally cleared drugs. These two alterations result in significantly improved renal function estimates compared with the standard CG formula. The CGopt approach has not previously been directly compared to MDRD.

Gentamicin is a highly water-soluble antibiotic that undergoes complete renal excretion via filtration, and is well suited as a marker of renal function [8]. Renal function as measured by inulin clearance was identical to gentamicin clearance (Cl\textsubscript{gent}) determined by two-point data (51.6 ml/min vs. 52.0 ml/min respectively) in hospitalised patients with stable renal function [9]. In a further study CrCl, as determined by 24 h urine collection, was virtually identical to Cl\textsubscript{gent} (126.1 ml/min and 124.4 ml/min respectively) [10].

This comparison was prompted by a need to determine which approach to renal function estimation was most suited for renally cleared drug dose calculation for our elderly inpatient population. Our objective was to compare CG\textsubscript{opt} with the MDRD approach for estimating renal function in a wide range of hospital inpatients, using Cl\textsubscript{gent} as a marker of renal function, with a view to assessing suitability for drug dosing purposes.

**Subjects and methods**

Patients receiving once-daily gentamicin therapy as part of routine inpatient treatment had blood samples drawn nominally at 2 and 14 h post-dose after the first or second dose. In order to avoid sampling during the distribution phase, the first sample was taken at least 2 h post-dose [11].

Doses were at the discretion of the prescribers, and gentamicin was administered intravenously over 5 min. Serum creatinine was measured from either the blood taken for gentamicin sampling, or a sample drawn within 24 h before or after the gentamicin dose.

**Inclusion criteria**

Patients above 18 years receiving once-daily gentamicin therapy.

**Exclusion criteria**

Patients with gentamicin concentrations <0.15 mg/l, dialysis, endocarditis, neutropenia, aminoglycoside allergy, pregnancy, critical illness, rapidly fluctuating renal function or cystic fibrosis.

Ethics’ committee approval was obtained at each hospital prior to commencement of patient recruitment and patients gave consent for study participation. The study was consistent with the principles of the Declaration of Helsinki. It was conducted across two general metropolitan teaching hospitals catering for medical and surgical patients, one specialising in care for the elderly.

**Patients**

Eighty-two patients consented to the study, with 68 patients eligible for analysis. Of the 14 ineligible patients four withdrew; gentamicin was ceased in one, blood samples were inadvertently not drawn in two and seven had gentamicin concentrations <0.15 mg/l. See Table 1 for patient characteristics. All patients had stable renal function at the time of study.

**Measurements**

CG\textsubscript{opt} was utilised to estimate CrCl [6]. The lesser of ideal or actual bodyweight was used, and serum creatinine was capped at a minimum value of 60 µmol/l (0.68 mg/dl). The abbreviated version of the MDRD formula was used for estimating GFR [3]. For comparative purposes MDRD values were adjusted for body surface area (BSA) using the formula (weight\(^{0.425}\) x (height\(^{0.725}\)) x 0.007184/1.73 as suggested [12].

Serum creatinine samples were quantified by the Jaffé method without deproteinisation, using a BM/Hitachi 717 (Hitachi Hitechnologies Corporation, Tokyo, Japan) and a solution of sodium hydroxide (800 mmol/l) and picric acid (25 mmol/l). Creatinine values were measured using assays that were aligned with isotope dilution-mass spectrometry in the interests of standardisation.

Serum gentamicin was quantified by Fluorescence Polarisation Immunoassay Analyzer (FPIA) (Abbott Diagnostics, Abbott Park, IL, USA) with an Abbott AxSYM gentamicin reagent pack.

Gentamicin clearance was calculated using standard one-compartment, first-order pharmacokinetics on a Microsoft Excel spreadsheet [13]. Student’s \(t\)-test was used for

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### Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>68</td>
<td>–</td>
</tr>
<tr>
<td>Hospital (RGH/FMC)</td>
<td>34/34</td>
<td>–</td>
</tr>
<tr>
<td>Male/Female</td>
<td>34/34</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.1 (8.3)</td>
<td>18.3–95.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75.5 (18.0)</td>
<td>38–130</td>
</tr>
<tr>
<td>Ideal weight (kg)</td>
<td>62.8 (10.9)</td>
<td>43.7–82.4</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>26.4 (5.6)</td>
<td>15.5–40.1</td>
</tr>
<tr>
<td>Daily gentamicin dose (mg/kg)</td>
<td>3.7 (1.1)</td>
<td>1.5–7.4</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>84 (31)</td>
<td>39–177</td>
</tr>
<tr>
<td>Gentamicin clearance (ml/min)</td>
<td>73.9 (29.9)</td>
<td>25.5–144.8</td>
</tr>
<tr>
<td>Optimised Cockcroft–Gault (ml/min)</td>
<td>64.9 (28.2)</td>
<td>18.7–142.9</td>
</tr>
<tr>
<td>MDRD\textsuperscript{*} (ml/min)</td>
<td>89.0 (33.0)</td>
<td>29.1–233.1</td>
</tr>
<tr>
<td>Non-optimised Cockcroft–Gault (ml/min)</td>
<td>82.5 (32.5)</td>
<td>18.7–172.2</td>
</tr>
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\textsuperscript{*}Body Surface Area calculated using \((\text{weight})^{0.425} \times (\text{height})^{0.725} \times 0.007184/1.73. \n
Figure 1. Percentage differences between MDRD and Cl\textsubscript{gent} (A) and between CG\textsubscript{opt} and Cl\textsubscript{gent} (B). Absolute differences (ml/min) between MDRD and Cl\textsubscript{gent} (C) and between CG\textsubscript{opt} and Cl\textsubscript{gent} (D).

Results

The patient characteristics are presented in Table 1.

Differences between MDRD and Cl\textsubscript{gent} versus age, and between CG\textsubscript{opt} and Cl\textsubscript{gent} are presented in Figure 1, as both the percentage difference (A and B) and the absolute difference in ml/min (C and D). Overall, CG\textsubscript{opt} underestimated renal function compared to Cl\textsubscript{gent} by 10%, and this was consistent across nominal age groups of <65, 65–80 and >80 years (see Appendix 1 in the supplementary data available at Age and Ageing online). MDRD overestimated renal function compared to Cl\textsubscript{gent} by 29%. MDRD increasingly overestimated renal function relative to Cl\textsubscript{gent}, increasing from 12 to 26 to 69% across the <65, 65–80 and >80 years groups respectively (P < 0.001). Capping serum creatinine at a minimum of 60 \(\mu\)mol/l (0.68 mg/dl) for MDRD caused the mean difference between MDRD and Cl\textsubscript{gent} to decrease to 23% for all patients, but the significant trend for increasing differences between MDRD and Cl\textsubscript{gent} across increasing age groups remained intact (P = 0.001). Patients were on average 12.7 kg heavier than their ideal bodyweight, subsequently reducing CG\textsubscript{opt} estimations by 17% compared to CG estimations without this adjustment. Fifteen patients had serum creatinine <60 \(\mu\)mol/l (0.68 mg/dl). Not capping the serum creatinine for CG\textsubscript{opt} marginally increased the renal function estimation by 2.3 ml/min, which was 6.4% less than the mean Cl\textsubscript{gent}.

For CG\textsubscript{opt} and MDRD, 94% and 79% of estimations were within 50% of Cl\textsubscript{gent} respectively (P = 0.001). For patients less than 65 years of age, 2 of 26 patients (8%) had MDRD estimations that were >50% of the Cl\textsubscript{gent} value, compared to 12 of 42 patients (29%) greater than 65 years of age (P = 0.056). For CG\textsubscript{opt}, all estimations for patients less than 65 years of age were within 50% of Cl\textsubscript{gent}, with four estimations (6%) >50% outside the equivalent Cl\textsubscript{gent} in patients greater than 65 years of age (two above and two below).

Linear regression analysis comparing CG\textsubscript{opt} renal function with Cl\textsubscript{gent} displayed a good correlation (\(r^2 = 0.55\), P < 0.001). MDRD renal function versus Cl\textsubscript{gent} resulted in a weaker correlation (\(r^2 = 0.35\), P < 0.001). This improved when serum creatinine was capped at a minimum of 60 \(\mu\)mol/l (0.68 mg/dl) (similar to CG\textsubscript{opt}) for calculations (\(r^2 = 0.48\), P < 0.001).

Characteristics of patients with MDRD that overestimated by 50% or more relative to Cl\textsubscript{gent} were compared to those where MDRD was within 50% of Cl\textsubscript{gent}. Analysis of variance was performed using age, weight, height and serum creatinine as variables (Table 2). The presence of lower serum
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Table 2. MDRD overestimations—50% or greater difference from CI\textsubscript{gent} versus within 50% of CI\textsubscript{gent}

<table>
<thead>
<tr>
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<th>50% or more than CI\textsubscript{gent}</th>
<th>Within 50% of CI\textsubscript{gent}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>14</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>73.3</td>
<td>62.9</td>
<td>0.059</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>6 (43)</td>
<td>28 (52)</td>
<td>0.56</td>
</tr>
<tr>
<td>Creatinine micromol/l (mg/dl)</td>
<td>64 (0.72)</td>
<td>90 (1.02)</td>
<td>0.005</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.1</td>
<td>169.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.8</td>
<td>78.5</td>
<td>0.006</td>
</tr>
</tbody>
</table>

creatinine and lower weight significantly influenced the overestimation of MDRD, while increasing age just failed to reach significance (P = 0.059). Half of the patients with overestimated MDRD values had a serum creatinine <60 \( \mu \text{mol/l} \) (0.68 mg/dl), which was the minimum input for serum creatinine values utilised in CG\textsubscript{opt}. An identical comparison was performed using MDRD estimations with a minimum serum creatinine value capped at 60 \( \mu \text{mol/l} \) (0.68 mg/dl), in order to bring it into parity with CG\textsubscript{opt}. With this adjustment, increasing age was the only variable with a significant impact on MDRD overestimation (P = 0.037).

Current recommendations suggest further investigation for CKD for any patient with an MDRD renal function of <60 ml/min/1.73 m\(^2\). MDRD predicted that 78% of this group had renal function >60 ml/min/1.73 m\(^2\). This was significantly higher than both CG\textsubscript{opt} and CI\textsubscript{gent} which predicted 44% and 57% of patients respectively (P < 0.001 and P = 0.010 respectively for comparison with MDRD). There was no difference between CG\textsubscript{opt} and CI\textsubscript{gent} (P = 0.12).

Discussion

The MDRD approach overestimated renal function in selected elderly patients when using CI\textsubscript{gent} as a baseline renal function indicator. This overestimation was age dependent and did not become apparent until after 65 years of age, a population that has rarely been studied for MDRD renal function estimation. Other groups have already noted the increasing disparity between MDRD and non-optimised CG estimates with increasing age, but due to the lack of an objective marker of renal function were unable to ascertain the extent to which either approach may have been at fault [14–16]. These investigators did, however, find differences of a similar incidence and magnitude in renal function estimations when comparing MDRD with CG in elderly populations [14, 15]. While increasing age appeared to drive this overestimation, the effect was variable and was not solely reliant on increasing age. A serum creatinine in the low-normal range as well as decreasing height and decreasing weight may also drive this effect [15, 16]. When all of these variables are simultaneously at extremes to those seen in the population that the MDRD equation was based on, the difference between MDRD compared to CG\textsubscript{opt} is greatest [16]. In this manner there may be a marked variation in the degree of overestimation by MDRD in elderly patients, ranging from negligible to clinically significant, and this may explain why the overestimation of MDRD in the elderly has gone largely un-noticed until now. In this study patients that were overestimated by 50% or more using MDRD were significantly lighter and with lower serum creatinine than those who were not, while increasing age just failed to be a significant influence. When MDRD was calculated using a minimum serum creatinine of 60 \( \mu \text{mol/l} \) (0.68 mg/dl), in order to bring it into parity with the way serum creatinine was utilised within the CG\textsubscript{opt} equation, only age was a significant variable for MDRD overestimation relative to CI\textsubscript{gent}.

Patients with >50% discrepancies between MDRD and CI\textsubscript{gent} in this study were on average 23 years older, 16 kg lighter, 5 cm shorter and with serum creatinine 113 \( \mu \text{mol/l} \) (1.28 mg/dl) lower than the population used by Levey et al. to develop the MDRD equation [2]. It may be unreasonable to expect MDRD to accurately predict renal function in this group of patients, who possess markedly different characteristics to the population it was developed in. On the background of an ageing population in the developed healthcare systems, it is essential the elderly are defined and studied as a group within their own right [17].

The CG\textsubscript{opt} equation, while underestimating renal function compared to CI\textsubscript{gent}, was not influenced by age. It was better suited as a marker to guide dose adjustment of renally cleared drugs in this population. The non-optimised CG equation estimates CI\textsubscript{Gr}, which is an overestimate of GFR, especially at low GFR values, due to the tubular secretion of creatinine. This was also the case in this study, but once the CG formula was corrected for bodyweight and the serum creatinine capped, the optimised version produced a renal function estimate lower than CI\textsubscript{gent} (P = 0.12).

This analysis showed that MDRD grossly overestimated renal function in a number of elderly patients, but not so for CG\textsubscript{opt}. While the mean absolute differences between MDRD and renal function were not huge (15 ml/min), the major differences were seen in the elderly, and these were often in the order of 30–50 ml/min. Overestimation of renal function by this amount has potentially huge ramifications for dosing in a patient whose baseline renal function is <50 ml/min. Renal function overestimation will result in relative overdosing of renally cleared drugs. The elderly are more likely to experience adverse drug events and be hospitalised longer for it [18]. Corsenello et al. demonstrated a doubling in the rate of adverse drug events for renally cleared drugs for patients with impaired renal function compared to those with normal renal function, driven by a lack of dose adjustment [19]. This makes MDRD unacceptable for calculating doses of renally cleared drugs in an elderly population. It has been shown that there would be huge increases in dosing for elderly patients compared to those in conventional practice should MDRD values be used as the basis for dosing [16]. While CG\textsubscript{opt} underestimated renal function in this group by 10%, this was more accurate than MDRD, and consistent across all ages,
hence better suited and safer for drug dosing purposes in this population.

There is an urgent need for further investigation of MDRD as an estimate of renal function in older hospitalised patients. The general acceptance of MDRD has been rapidly accelerated due to its automatic generation on all laboratory reports containing a serum creatinine value. This has occurred especially in the hospital setting where serum creatinine is often ordered on a daily basis. Current recommendations indicate that MDRD should not be used for drug dose calculation, and this is supported by our study. Use of MDRD in the hospitalised elderly would lead to inadvertent overdosing if used for such a purpose.

Very low serum creatinines (<60 µmol/l (0.68 mg/dl)) are occasionally seen in the elderly. Use of these very low serum creatinine values to estimate renal function invariably results in gross overestimates. For this reason a minimum cap on serum creatinine has been suggested [4, 6, 20]. This approach has led to better estimates of renal function and should be investigated as a possible means of improving the accuracy of MDRD. Capping the serum creatinine in this group for MDRD improved its ability to estimate renal function when using Cl\text{gent} as a marker. It did not however significantly alter the overestimation in renal function by MDRD in the elderly patients.

This study is limited by relatively small numbers and the use of Cl\text{gent} as a comparator. Gentamicin is an accurate indication of renal function, but is not considered a gold standard [9, 10]. The study needs to be reproduced in a larger population using gold-standard renal function measures. Only the abbreviated form of the MDRD equation was used in this comparison.

The CG\text{opt} method of renal function estimation is the preferred approach for determining doses of renally cleared drugs in a hospitalised population containing elderly patients. The abbreviated version of the MDRD equation overestimates renal function in a clinically significant proportion of elderly patients, making its use potentially dangerous for this purpose. This may also hinder the screening accuracy of MDRD in this population.

Key points

- MDRD grossly overestimates renal function in selected elderly patients.
- MDRD renal function estimations should not be used to calculate drug doses in the elderly.
- A modified version of Cockcroft–Gault was best suited for drug dose calculations in the elderly.

Acknowledgements

Gregory W. Roberts—design, data analysis, manuscript preparation. Pernille M. Ibsen—design, data collection, manuscript preparation. Charlotte Teglman—design, data collection, manuscript preparation.

Conflicts of interest

The results presented in this paper have not been published previously in whole or part, except in abstract form. None of the authors have any conflicts of interest, financial or otherwise.

Supplementary data

Supplementary data are available online at Age and Ageing online.

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Perceptions of active ageing in Britain: divergences between minority ethnic and whole population samples

ANN BOWLING

Perceptions of active ageing in Britain: divergences between minority ethnic and whole population samples

Abstract

Objective: to identify perceptions of, and associations with, active ageing among ethnically diverse and homogeneous samples of older people in Britain.

Design and setting: cross-sectional and longitudinal surveys of older people living at home in Britain.

Measures: active ageing, health, psych-social, socio-economic circumstances, and indicators of quality of life.

Results: respondents defined active ageing as having health, fitness, and exercise; psychological factors; social roles and activities; independence, neighbourhood and enablers. The ethnically diverse sample respondents were less likely to define active ageing as having physical health and fitness, and were less likely to rate themselves as ageing actively, than more homogeneous sample respondents. The lay-based measure of quality of life used was independently and consistently associated with self-rated active ageing in each sample.

Conclusion: policy models of active ageing were reflected in lay views, although the latter had a more multidimensional focus. Lay definitions of active ageing were also more dynamic, compared with definitions of quality of life and successful ageing. Differences in self-rated active ageing and perceptions of this concept by ethnic group need further exploration.

Keywords: active ageing, ethnicity, old age, quality of life, successful ageing, elderly