Estimating Glomerular Filtration Rate in Black South Africans by Use of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations

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BACKGROUND: The 4-variable Modification of Diet in Renal Disease (4-v MDRD) and Cockcroft-Gault (CG) equations are commonly used for estimating glomerular filtration rate (GFR); however, neither of these equations has been validated in an indigenous African population. The aim of this study was to evaluate the performance of the 4-v MDRD and CG equations for estimating GFR in black South Africans against measured GFR and to assess the appropriateness for the local population of the ethnicity factor established for African Americans in the 4-v MDRD equation.

METHODS: We enrolled 100 patients in the study. The plasma clearance of chromium-51–EDTA (51Cr-EDTA) was used to measure GFR, and serum creatinine was measured using an isotope dilution mass spectrometry (IDMS) traceable assay. We estimated GFR using both the reexpressed 4-v MDRD and CG equations and compared it to measured GFR using 4 modalities: correlation coefficient, weighted Deming regression analysis, percentage bias, and proportion of estimated GFR within 30% of measured GFR (P30).

RESULTS: The Spearman correlation coefficient between measured and estimated GFR for both equations was similar (4-v MDRD $R^2 = 0.80$ and CG $R^2 = 0.79$). Using the 4-v MDRD equation with the ethnicity factor of 1.212 as established for African Americans resulted in a median positive bias of 13.1 (95% CI 5.5 to 18.3) mL/min/1.73 m$^2$. Without the ethnicity factor, median bias was 1.9 (95% CI −0.8 to 4.5) mL/min/1.73 m$^2$.

CONCLUSIONS: The 4-v MDRD equation, without the ethnicity factor of 1.212, can be used for estimating GFR in black South Africans.

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Globally, chronic kidney disease (CKD)4 is recognized as an important public health problem (1). In South Africa, the high prevalence of hypertension, diabetes, and infection with HIV results in a significant risk for CKD (2); it is therefore important to detect kidney dysfunction as early as possible in this population. Current guidelines define CKD as the presence, for 3 or more months, of either kidney damage as defined by structural or functional abnormalities of the kidney or a glomerular filtration rate (GFR) <60 mL/min/1.73 m$^2$ (3, 4). GFR, an important component in the diagnosis of CKD, is also accepted as the best overall measure of kidney function (3, 5). Individuals with decreased GFR are at increased risk not only for the development of end-stage renal failure, but also for hospitalizations, cardiovascular disease, and other complications of decreased kidney function (6–10). It has been shown that early detection, appropriate evaluation, and management of CKD improves outcome (1, 3, 4).

GFR can be measured as the renal clearance of exogenous markers such as inulin, chromium-51–EDTA ($^{51}$Cr-EDTA), technetium-labeled diethylene-triamine-pentacetate ($^{99m}$Tc-DTPA), and iohexol. These exogenous markers are impractical for routine use, however. Endogenous GFR markers include creatinine and cystatin C. Creatinine is the most commonly used marker in the clinical laboratory to assess GFR, but it

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4 Nonstandard abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; $^{51}$Cr-EDTA, chromium-51–EDTA; eGFR, estimated GFR; S-Cr, serum creatinine; 4-v MDRD, 4-variable Modification of Diet in Renal Disease; CG, Cockcroft-Gault; IDMS, isotope dilution mass spectrometry; CrCl, creatinine clearance; BSA, body surface area; mGFR, measured GFR; IQR, interquartile range.
has multiple limitations (11)—for example, it is also affected by factors such as muscle mass, diet, sex, and age (12, 13).

To overcome some of these limitations, the National Kidney Foundation—Kidney Disease Outcomes Quality Initiative and Kidney Disease: Improving Global Outcomes guidelines recommend the estimation of GFR (eGFR) using prediction equations based on serum creatinine (S-Cr) (3, 4). The 2 most commonly used prediction equations are the 4-variable Modification of Diet in Renal Disease (4-v MDRD) (14) and Cockcroft-Gault (CG) (15) equations. The MDRD equation was derived in the United States by analysis of data from 1628 patients (651 women and 195 African-Americans) with known kidney disease using $^{125}$I-iothalamate clearance to measure GFR as the reference procedure (mean GFR 40 mL/min/1.73 m$^2$) and was based on 6 variables: age, sex, serum creatinine, urea, albumin, and ethnicity (16). Subsequently, a 4-v MDRD equation based on 4 variables—age, sex, serum creatinine, and ethnicity—was proposed to simplify its use in the clinical environment (14). An ethnicity factor of 1.212 was established for African Americans (14, 16).

Because of variability in serum creatinine assays, the National Kidney Disease Education Program Laboratory Working Group initiated a creatinine standardization program with creatinine calibration traceable to isotope dilution mass spectrometry (IDMS) creatinine measurement (17). The 4-v MDRD equation was reexpressed for use with the IDMS traceable creatinine measurements (18).

The Cockcroft-Gault equation was derived from 236 hospital inpatients in Canada (4% women, ethnicity not stated) with measured creatinine clearance (CrCl) as the reference procedure (mean CrCl 73 mL/min) (15).

Neither of these formulae nor the ethnicity factor of 1.212 established for African Americans has yet been evaluated in African or non-American black populations. The applicability of these equations and the factor for ethnicity to black South Africans is therefore unknown. The aim of this study was to examine the applicability of the 4-v MDRD and CG equations for estimating GFR in black South Africans against measured GFR and to evaluate whether the ethnicity factor established for African Americans is appropriate for black South Africans.

Materials and Methods

Participants
We conducted a prospective study of patients seen at Chris Hani Baragwanath Hospital in 2006. Participants, who were recruited after being screened and counseled by their clinicians, were older than 18 years and had established CKD or risk factors for developing CKD, such as hypertension, diabetes, and HIV. Exclusion criteria were pregnancy, acute kidney injury, and edema. We enrolled 100 black South Africans with varying degrees of renal function. All participants gave informed consent after being educated with regard to potential benefits, risks, and study procedures. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand.

Test Methods
Age (years), standing height (centimeters), weight (kilograms), and sex were recorded for all participants. Before GFR measurement, we collected a 5-mL blood sample for serum creatinine measurement using an alkaline picrate rate-blanked compensated kinetic assay (Roche Modular analyzer; Roche Diagnostics) with calibration traceable to IDMS. To assess possible calibration differences, we used a calibration panel of 40 serum samples (Cleveland Clinic Foundation), with values assigned by a Roche enzymatic assay (Creatinine Plus; Roche Diagnostics), that has been independently validated as traceable to IDMS (19).

GFR Measurements
We used $^{51}$Cr-EDTA plasma clearance as a reference method for measuring GFR. GFR was measured according to guidelines adopted by the British Nuclear Medicine Society (20) and calculated with the slope intercept method (21), corrected with the Brochner-Mortensen equation (22), and normalized to body surface area (BSA) using the DuBois method: BSA (m$^2$) = [71.84 × weight (kg)$^{0.425}$ × height (cm)$^{0.725}$] / 10 000 (23). This value is referred to as measured GFR (mGFR). (For a detailed description of the GFR measurements, see the Data Supplement that accompanies the online version of this article at www.clinchem.org/content/vol54/issue7.)

GFR Estimations
GFR was estimated using the following equations:

- reexpressed 4-v MDRD equation (18, 24): eGFR (mL/min/1.73 m$^2$) = 175 × [S-Cr (μmol/L)/88.4]^{-1.154} × age (years)^{-0.203} × (0.742 if female) × (1.212 if African American)

- Cockcroft-Gault equation (15) normalized to 1.73 m$^2$: eGFR (mL/min/1.73 m$^2$) = [(140 − age in years) × weight (kg) × (0.85 if female) × 1.73 (m$^2$)]/[S-Cr (μmol/L) × 0.814 × BSA (m$^2$)]
To assess the validity of the 4-v MDRD equation with the African American factor in the black South African population, GFR was estimated both with and without this factor. The CG equation was normalized to 1.73 m² to allow comparison with the 4-v MDRD equation and measured GFR. This is in keeping with most studies but is unlikely to reflect standard clinical practice (25). Because the CG equation was developed with CrCl as the reference procedure and a creatinine assay not traceable to current IDMS values, bias is to be expected for the CG equation. To minimize this bias, we established a correction factor for the CG equation, determined from the dataset of 100 patients by minimizing the sum of the squared residuals (the difference between eGFR and mGFR).

STATISTICAL METHODS

Statistical analysis was conducted using Analyze-it for Microsoft Excel. We used the Shapiro-Wilk test to test for normality. Continuous data variables are expressed as mean (SD) if parametric and median [interquartile range (IQR)] if nonparametric. We assessed the performance of the 4-v MDRD equation, both with and without the ethnicity factor, and the Cockcroft-Gault equation normalized to 1.73 m² relative to that of mGFR by use of Spearman correlation coefficient, weighted Deming regression analysis, median percentage difference between estimated and measured GFR (percentage bias), and proportion of eGFR within 30% of mGFR (P30). We used weighted Deming regression analysis to take into account random error in both measured GFR and serum creatinine measurement (24).

Results

PARTICIPANTS

Between August 2006 and November 2006, 100 black South Africans (51 men and 49 women) were enrolled in the study. All participants were inpatients at the Chris Hani Baragwanath hospital or were being followed up at the renal unit outpatient department at the hospital. The study population had a median (IQR) age of 47 (26) years, range 18–86 years. Participants suffered from a wide range of different diseases, the most common of which included hypertension (n = 36), diabetes (n = 25), and HIV (n = 20). Other diagnoses included renal calculi, deep venous thrombosis, meningitis, multiple myeloma, nephrotic syndrome, and epilepsy. Participants being worked up for possible kidney donation were also included (n = 7). The median mGFR was 61.5 (49.6) mL/min/1.73 m², range 3–132 mL/min/1.73 m². (See Supplemental Table 1.)

CREATININE CALIBRATION

Evaluation of S-Cr calibration was based on 39 observations, after excluding one of the samples with a difference between the assigned value and the measured value of >3 SDs from the mean difference. The measurements were done in triplicate in 3 separate runs, with measured S-Cr values ranging from 44 to 398 μmol/L. The correlation between the Cleveland Clinic Foundation (CCF) assigned values and the South African (SA) measured values was high (R² = 0.999). Deming regression analysis was used to calculate the slope, 0.964 (95% CI 0.952 to 0.975), and intercept, 0.039 (95% CI 0.010 to 0.068), of the regression equation, with y = CCF-assigned values and x = SA-measured values. Because of this small but significant regression slope, measured S-Cr (SA) values were standardized to CCF values with the following equation: standardized S-Cr = 0.039 + [0.964 × S-Cr (SA)]. Standardized S-Cr values were used in all calculations.

COMPARISON OF MEASURED GFR TO THE 4-v MDRD EQUATION

The Spearman correlation coefficient between mGFR and the 4-v MDRD equation was 0.90 (95% CI 0.85 to 0.93). Weighted Deming regression analysis showed a significant proportional bias of 1.24 (95% CI 1.09 to 1.38, P = 0.001) but no significant constant bias [0.24 (95% CI −5.91 to 5.43, P = 0.93)] when the established ethnicity factor of 1.212 was used. Without the ethnicity factor, weighted Deming regression analysis showed no significant proportional bias [1.02 (95% CI 0.90 to 1.14, P = 0.73)] or constant bias [0.02 (95% CI −4.61 to 4.65, P = 0.99)]. The percentage bias (median percentage difference between eGFR and mGFR) for the 4-v MDRD equation with the established ethnicity factor of 1.212 was 27%. Without the ethnicity factor, percentage bias was 5%. With the ethnicity factor of 1.212, P30 for the 4-v MDRD equation was 52% vs 74% without the ethnicity factor (Fig. 1).

COMPARISON OF MEASURED GFR TO THE CG EQUATION

The Spearman correlation coefficient between mGFR and CG normalized to 1.73 m² was 0.89 (95% CI 0.85 to 0.93). Weighted Deming regression analysis comparing the CG equation to mGFR showed a significant proportional bias of 1.13 (95% CI 1.03 to 1.23, P = 0.01) but no significant constant bias [2.38 (95% CI −1.37 to 6.13, P = 0.21)]. Percentage bias for the CG equation was 19%, and P30 was 58%. The factor calculated to minimize bias of the CG equation in this dataset was 0.82 (95% CI 0.78 to 0.85). Correcting the CG equation for bias, eGFR (mL/min/1.73 m²) = 0.82 × CG (mL/min/1.73 m²), improved P30 to 71%.
PERFORMANCE OF EQUATIONS AT DIFFERENT STAGES OF RENAL DISEASE

For each of the eGFR equations, the dataset was split into 3 groups: eGFR <30, 30–60, and >60 mL/min/1.73 m². In each of these groups, the median difference between eGFR and mGFR (bias), percentage bias, IQR of the difference between eGFR and mGFRs, and root mean squared error were calculated. For each of the equations, bias, IQR, and root mean squared error increased at higher levels of eGFR (Table 1).

Discussion

CKD is increasingly recognized as a global public health problem (1). The high prevalence of hypertension, diabetes, and HIV in sub-Saharan Africa has resulted in a high risk for CKD (2). Early detection of CKD using simple laboratory tests and GFR prediction equations, such as the CG and 4-v MDRD equations, is important for the prevention of long-term complications.

Neither the CG nor the 4-v MDRD equation has previously been validated in Africa. The 4-v MDRD equation has also not been validated in a black population with a different body habitus than that of African Americans. Our results show that both the CG (after correcting for bias) and the 4-v MDRD (without the ethnicity factor established for African Americans) can be used for estimating GFR in black South Africans.

Many recent articles have underscored the importance of creatinine standardization (17). For this study, we used an alkaline picrate rate-blanked compensated kinetic assay (Roche Diagnostics) with calibration traceable to IDMS. In a study by Miller et al. (26), this method showed minimal bias compared with an IDMS value. We also assessed and corrected for possible calibration differences by using a calibration panel with values assigned by the Roche enzymatic assay (Cleveland Clinic Foundation). Because the S-Cr results were traceable to IDMS, we used the reexpressed 4-v MDRD equation (14).

The correlation coefficient for the 4-v MDRD equation was similar those of studies done in other population groups (27–29). The 4-v MDRD equation using the ethnicity factor of 1.212 as suggested for African Americans overestimated mGFR in black South Africans. Without the ethnicity factor (thus using the same equation as established for whites in the MDRD study), median overestimation was minimal and there was no significant proportional bias. Accuracy within 30% of mGFR was 52% with the ethnicity factor of 1.212 and 74% without the ethnicity factor.

Goldwasser et al. (30) showed that African Americans have higher renal creatinine excretion per kilogram body weight than whites and concluded that this may be related to differences in body composition, muscle metabolism, or diet. Lewis et al. (31) showed higher serum creatinine levels and urinary creatinine excretion rates for a given GFR in African Americans compared with non-African Americans. This may not be true for black South Africans, as the 2 populations have different origins (32).

Creatinine generation is determined primarily by muscle mass and dietary intake (6). Differences in the ethnicity factor established for African Americans and black South Africans may be attributed to differences in muscle mass and body composition as well as differences in diet. Various studies have shown that West African athletes have less body fat and thicker thighs than whites, and this difference is even more striking between East and West Africans (33). Mean weight and BSA for the MDRD study population were 79.6 (16.8) kg and 1.91 (0.23) m², respectively (16); for the MDRD African American study population, 84.1 kg and 1.96 m² (31); for the African-American Study of Kidney disease and hypertension (AASK), 90.2 kg and 2.02 m².
Differences in dietary intake are difficult to quantify, but it is likely that black South Africans consume less creatinine-generating food than African Americans owing to poorer socioeconomic circumstances. The CG equation is still commonly used for estimating creatinine clearance as an indicator of GFR and was therefore included in the analysis. The correlation coefficient for the CG equation was similar to those of studies done in other population groups. The positive bias observed for the CG equation may be attributed to the CG equation being established using creatinine clearance as a reference procedure, which overestimates GFR owing to the tubular secretion of creatinine. It may also be attributed to calibration biases between creatinine measurement for the original CG study and this study, as well as the CG equation being established in a different population group.

The study population included 20 patients who were known to be infected with HIV. In South Africa, the Nelson Mandela/Human Sciences Research Council survey estimated the prevalence of HIV in the adult population (15–49 years old) to be 15.6% (34). Chronic kidney disease is increasingly being recognized as an important complication of HIV infection (35), and the estimation of GFR in this population group is therefore important. Further studies are needed to evaluate the performance of the 4-v MDRD equation in patients infected with HIV.

Limitations of the study were as follows: a) The study has a relatively small sample size. b) It was conducted at only one geographical site, which does not adequately represent all population groups in South Africa. Further studies for these population groups are needed. c) The characteristics of the study population differed from that of the MDRD study population. The study population included hospitalized patients and participants who were known to be infected with HIV. In these participants, creatinine production may differ and they may have reduced creatinine excretion compared with the MDRD study population, which consisted of outpatients with CKD who were otherwise healthy. d) In this study, plasma sampling was done at 2 and 4 h for patients with eGFR > 30 mL/min/1.73 m².

Table 1. Performance of equations.\(^{a}\)

<table>
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<tr>
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<th>eGFR</th>
<th>n</th>
<th>Median bias, mL/min/1.73 m² (95% CI)</th>
<th>Median percentage bias, %</th>
<th>IQR, mL/min/1.73 m²</th>
<th>RMSE, mL/min/1.73 m²</th>
<th>P(^{30}) %</th>
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<td>20</td>
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<td>eGFR 30–60 mL/min/1.73 m²</td>
<td>15</td>
<td>8.8 (–2.2 to 14.8)</td>
<td>23.8</td>
<td>15.7</td>
<td>18.0</td>
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<td></td>
<td>eGFR &gt;60 mL/min/1.73 m²</td>
<td>65</td>
<td>20.4 (17.6 to 28)</td>
<td>28.8</td>
<td>28.6</td>
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<td>Overall</td>
<td>100</td>
<td>13.1 (5.5 to 18.3)</td>
<td>27.0</td>
<td>25.2</td>
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<td>5.1 (–0.3 to 17.0)</td>
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<td>100</td>
<td>1.9 (–0.8 to 4.5)</td>
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<td>16.4</td>
<td>16.6</td>
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<td>6.0 (0.1 to 14.6)</td>
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<td>–2.4</td>
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\(^{a}\) IQR is the difference between estimated and measured GFR. RMSE (root mean squared error) was calculated as the square root of [(median difference in estimate – measured)^2 + (IQR of the difference)^2]. P\(^{30}\) is accuracy within 30% of measured GFR.
and at 3 and 5 h for patients with eGFR < 30 mL/min/1.73 m². Using the renal clearance of ⁵¹Cr-EDTA as a reference procedure, Brochner-Mortensen and Freund (36) showed that in patients with advanced chronic kidney disease (GFR 3–13 mL/min) plasma sampling done at 4 and 24 h after injection is more reliable [0.5 (0.5) mL/min] than that done between 3 and 5 h [3.7 (2.2) mL/min]. In the South African context, however, delayed plasma sampling may have resulted in patients being lost to follow up. e. The Cleveland Clinic calibration panel and participant samples were run at different times. A residual calibration error is therefore still possible.

In summary, our study confirms that both the 4-v MDRD equation, without the ethnicity factor of 1.212, and the Cockcroft-Gault equation, after correcting for bias, can be used for estimating GFR in black South Africans.

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