

Comparison of Creatinine Clearance Estimates with Routine Measured Clearance in Adult Jordanians

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Abstract

Aims: To determine the correlation between endogenous creatinine clearance, the Modification of Diet in Renal Disease and Cockcroft–Gault equations, and to examine agreement between these methods.

Material and Method: Creatinine clearance measured by 24-hour urine creatinine in patients with chronic kidney disease was compared with estimated clearance using the Cockcroft–Gault and Modification of Diet in Renal Disease equations. Correlation, regression analysis, limits of agreement and concordance analysis were used.

Results: There was a positive correlation between both the Cockcroft-Gault ($r=0.931$, $p<0.001$) and the Modification of Diet in Renal Disease ($r=0.741$, $p<0.001$) equations with creatinine clearance; the former being statistically superior ($P = 0.0073$) comparing the correlation coefficients. Using Bland-Altman method, there was better agreement with the Cockcroft–Gault formula where the limits of agreement were (-10.1 to +11.2) compared with (-22.8 to +18.5) for the Modification of Diet in Renal Disease. Concordance analysis showed a concordance correlation coefficient of 0.938 (95% CI, 0.89-0.97) for Cockcroft-Gault and 0.713 (95% CI, 0.55-0.82) for Modification of Diet in Renal Disease. Pearson ρ coefficient (precision) and bias correlation factor C_b (accuracy) of Cockcroft–Gault were 0.939, 0.998 and of Modification of Diet in Renal Disease they were 0.713 and 0.947, respectively.

Conclusions: In Jordanian patients, the Cockcroft–Gault equation had a superior performance in the estimate of creatinine clearance compared to the Modification of Diet in Renal Disease equation. Further studies to evaluate these formulae with larger number of patients and using a gold standard method are needed. In the meantime, we suggest using the Cockcroft–Gault equation in patients with a moderate-to-severe chronic renal failure.

Keywords: Creatinine, Clearance, Cokroft-Gault, MDRD, Jordan.

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Introduction

A 24-h urine collection to determine the creatinine clearance (CrCl) is a widely used

method for the assessment of glomerular filtration rate (GFR) in clinical practice, because it is more accurate than the serum creatinine concentration alone.^{1,2}

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However, this method is cumbersome, inconvenient and often difficult to collect a complete 24-h urine sample accurately,^{3, 4} especially in the out-patient setting.

Two study equations, the Cockcroft–Gault (CG)⁵ and the Modification of Diet in Renal Disease (MDRD),^{6, 7} are currently widely used to estimate GFR. Indeed, the National Kidney Foundation's K/DOQI guidelines consider both the CG and the MDRD equations reliable measures for GFR in adults.⁸

Prediction equations need to be validated for the population in which they are to be used. Racial differences affect serum creatinine because of differences in muscle mass and renal handling of creatinine.⁹ There is still a paucity of published data on the applicability of the CG and MDRD formulae in many ethnic groups other than Caucasians and African-Americans; the groups from which these equations were originally derived.

This study will assess, in a cohort of Jordanian patients, the performance of the CG and the MDRD equations, by utilizing measured CrCl as the gold standard.

Subjects and Methods

The medical records of seventy nine patients with chronic kidney disease, attending the nephrology outpatient clinic at Jordan University Hospital, were reviewed. The adequacy of the 24-h urine collection was assessed by comparing the total urine Creatinine (mg/24hr) in the sample to the predicted creatinine $[22 - (\text{age}/9)] * \text{kilogram of body weight in women}$ and $[28 - (\text{age}/6)] * \text{kilogram of body weight in men (mg/24hr)}$.¹⁰ Collections in which the difference between the predicted 24-h urine creatinine and the measured 24-h urine creatinine was more than 20% were defined as under-collection. Likewise, collections in which the difference between the measured 24-h urine creatinine and the predicted 24-h urine creatinine was greater than 20% and they were defined as over collections. The under and over-collections were excluded from the study.

Forty four patients (31 men and 13 women) with adequate 24-h urine collection were ultimately included. Their average age was 61.38 ± 15.28 years. The mean serum creatinine at the time of this study was 2.14 ± 0.93 mg/dl. Based on measured CrCl, 65.9% of patients had stage III and 27.7% had stage IV chronic kidney disease. The concentration of serum and urine creatinine was measured by a creatinine picric acid Jaffé colorimetric test using Roche/Hitachi 917 analyzer.

The accurate 24-h urine collections were used to calculate CrCl according to the CrCl equation: $\text{CrCl (ml/min)} = (\text{urine creatinine (mg/dl)} * 24\text{-h urine volume (ml)}) / (\text{serum creatinine (mg/dl)} * 1440)$. Four-variable MDRD equation was used,⁷ where $\text{MDRD-GFR (mL/min/1.73m}^2) = 186.3 * \text{serum creatinine (mg/dl)}^{-1.154} * \text{age (year)}^{-0.203} * 1.212$ if African American * 0.742 if female.

The Cockcroft–Gault equation;⁵ $\text{CG-GFR (ml/min)} = \{ [140 - \text{age (year)}] * \text{weight (kilogram)} / [72 * \text{serum creatinine (mg/dl)}] \} * 0.85$ if female).

Statistical Analysis

MedCalc statistical software version 9.4.2.0 was used for the statistical analysis. Correlation was performed using the Spearman's rank test. Comparison between two correlation coefficients from independent samples was tested using Fisher z test. Linear regression analysis was used. The limits of agreement between the two methods were analyzed by the Bland-Altman method. Concordance analysis was performed to look at precision and accuracy of formulae.

Results

The mean creatinine clearance for CG, MDRD and CrCl was 41.35 ± 15.77 , 38.45 ± 11.96 and 40.61 ± 16.03 , respectively. There was a very good correlation between CrCl and CG ($r=0.931$, $p<0.001$), (Figure 1a). The correlation of MDRD and CrCl was lower than that for CG ($r=0.741$, $p<0.001$), (Figure 1b), with the difference between these correlation coefficients being significant ($P = 0.0073$).

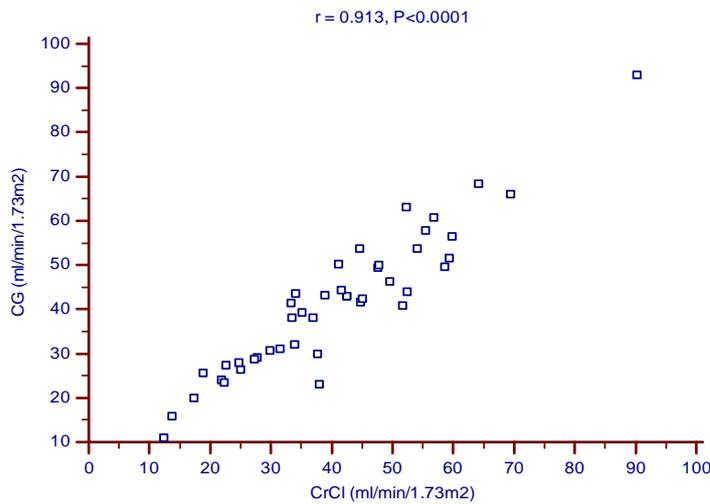


Figure (1a).

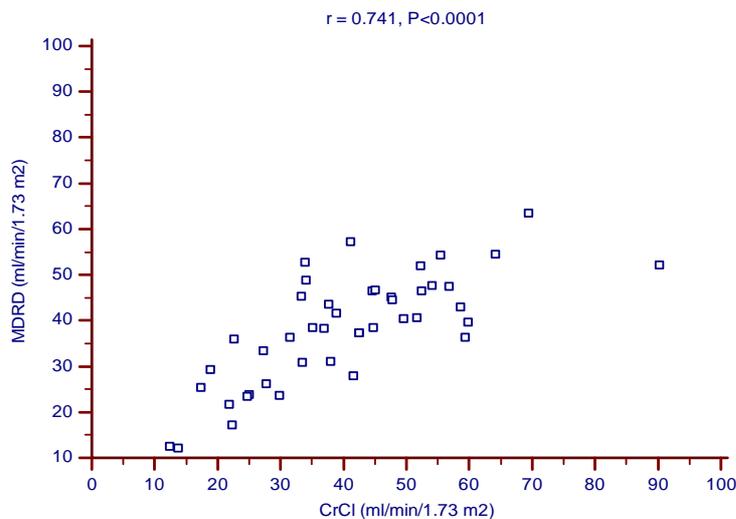


Figure (1b).

Figure (1): (a) Correlations between 24-hour urinary creatinine clearance with that estimated using the CG. (b) Correlations between 24-hour urinary creatinine clearance with that estimated using the MDRD.

Figure (2) shows the linear regression analysis with the coefficient of determination and the regression formulae for CG and MDRD. The (r^2) was higher for the CG compared with MDRD. The root of mean square of residual was 5.46 for CG compared to 7.97 for the MDRD, indicating better fit of CG.

Using Bland-Altman method, there was acceptable limits of agreement for the CG with limits of (-10.1 to +11.2), whereas the limits of agreement for MDRD were wider (-22.8 to +18.5) (Figure 3).

When data was log transformed, the limits of agreement were -0.115 to +0.137 for CG and -0.22 to +0.19 for MDRD. (Figure 4). For CG formula, about 95% of the cases, the CrCl would be between 0.76 and 1.37 times the estimated values indicating that the measured CrCl might differ from CG formula by 24% below to 37% above. For MDRD, about 95% of the cases, the CrCl would be between 0.6 and 1.54 times the estimated values indicating that the measured CrCl might differ from MDRD formula by 40% below to 54% above.

Concordance analysis showed a concordance correlation coefficient of 0.938 (95% CI, 0.89-0.97) for Cockcroft-Gault and 0.713 (95% CI, 0.55-0.82) for MDRD.

Pearson ρ coefficient (precision) and bias correction factor C_b (accuracy) of CG were 0.939, 0.998 and those of MDRD were 0.713, 0.947, respectively.

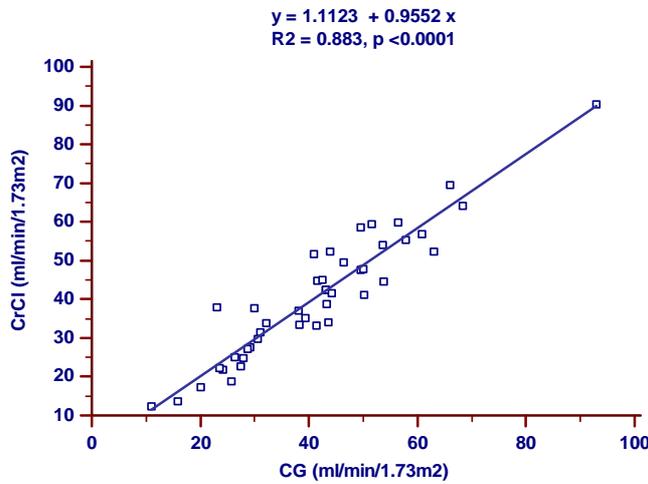


Figure (2a).

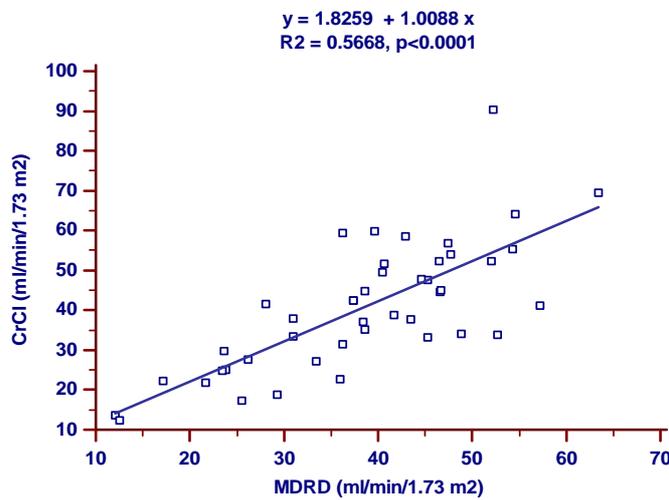


Figure (2b).

Figure (2): (a) Linear regression model tested for the relation between the CG and CrCl. (b) Linear regression model tested for the relation between the MDRD and CrCl.

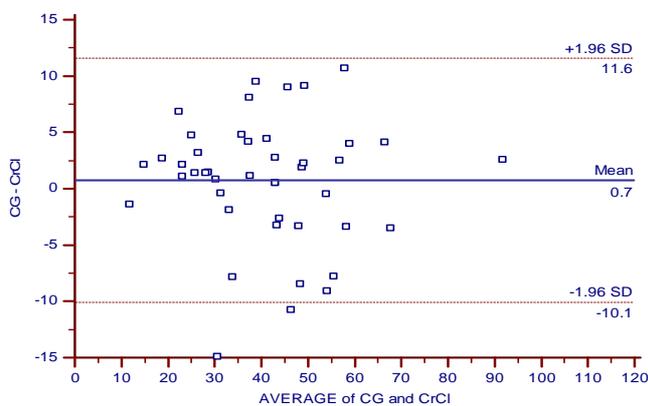


Figure (3a).

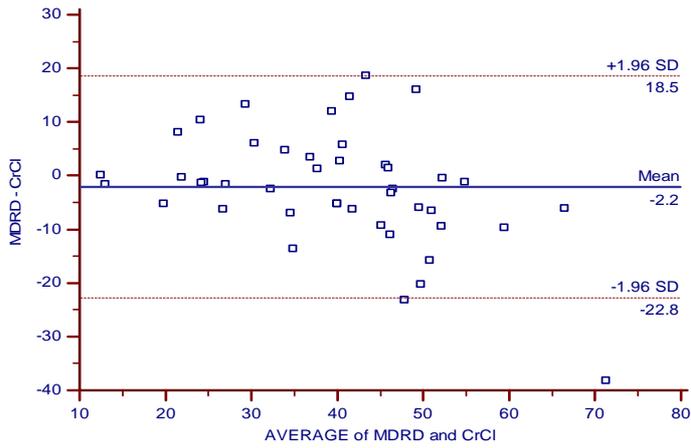


Figure (3b).

Figure (3):(a) Bland-Altman plot showing the agreement between CG and CrCl. (b) Bland-Altman plot showing the agreement between MDRD and CrCl.

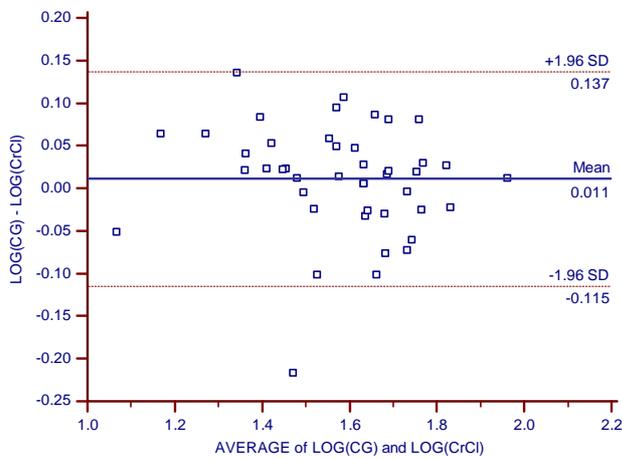


Figure (4 a).

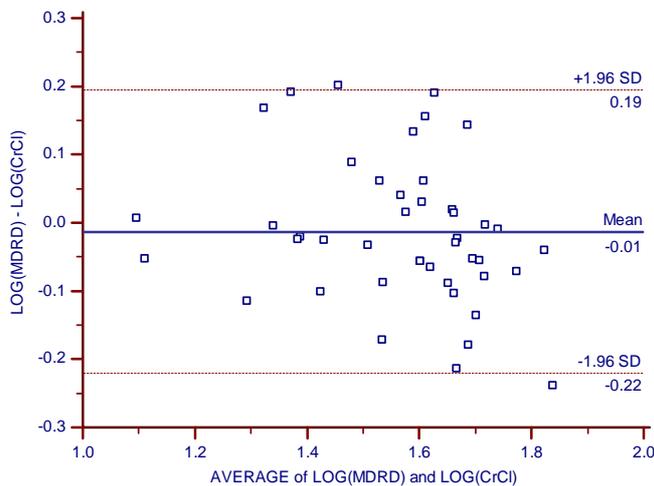


Figure (4b).

Figure (4): (a) Limits of agreement of log transformed CG and CrCl. (b) Limits of agreement of log transformed MDRD and CrCl.

Discussion

The National Kidney Foundation's K/DOQI guidelines consider the CG and the MDRD equations reliable measures for GFR in adults.¹⁰ The applicability of the MDRD and CG equations has been studied in the normal population¹¹⁻¹³ and in general chronic kidney disease.^{13,14} The present study is the first to apply these equations in adult Jordanians. The findings of the present study also showed a very good correlation between CrCl and both CG and MDRD.

From an analysis of bias, a measure of systematic error, we found that the MDRD GFR estimate was 2.2 mL/min/1.73m² lower than that of CrCl and the CG GFR was 0.7 mL/min/1.73m² higher. This result is consistent with previous studies in patients with chronic kidney disease which found that the MDRD equation underestimates while CG overestimates the GFR. The bias of the MDRD equation was 9.0 mL/min/1.73m² lower and CG equation 1.9 mL/min/1.73m² higher than ¹²⁵I Iothalamate clearance,¹³ and 1.0 mL/min/1.73m² lower and CG equation 1.94 mL/min/1.73m² higher than chromium-51 ethylenediamine tetraacetic acid (51Cr-EDTA) clearance.¹⁴

The present study provides evidence that in the entire group of patients, the CG equation had less bias, was more precise and was more accurate than the MDRD equation when using CrCl as a gold standard. This may be expected by the fact that the CG has a weight variable, which is not present in MDRD. Weight is a more direct measure of muscle mass in individual patients than the ethnicity, gender and age variables in MDRD. In our patients, muscle mass and hence weight can vary significantly based on the state of their disease and nutrition.

The present study has limitations. First, this study used CrCl as a gold standard measurement for estimated GFR. To date, there are many accepted accurate methods for estimated GFR, including inulin,¹⁵ 51Cr-EDTA,¹⁶⁻¹⁸ ¹²⁵I-iothalamate,¹⁹⁻²¹ iohexol clearance²² and ^{99m}Tc-DTPA.²³

However, these methods are expensive and available mainly in research settings. In one study CrCl was 10–15% higher than the inulin clearance rate, but fortunately, this error is balanced by an error of almost equal magnitude in the measurement of the serum creatinine by the Jaffé colorimetric assay.²⁴ However, CrCl is the most common measurement of GFR in daily clinical practice. Secondly, the CG formula was derived from CrCl measurements and that could explain some of its better correlation.

In conclusion, the CG equation had superior performance in the estimate of CrCl than the MDRD equation in Jordanian patients. There is clearly a need for research to evaluate the CG and MDRD prediction equations in adult Jordanians including larger number of patients, but a gold standard method must be used for comparison. In the meantime, we suggest using the CG equation in Jordanian patients.

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