Modification of Diet in Renal Disease Equation Underestimates Glomerular Filtration Rate in Egyptian Kidney Donors

Salwa Ibrahim,[1] Laila Rashid[2]

Abstract

Objectives: **Inulin clearance and radioisotope studies are the most accurate means of measuring glomerular filtration rates (GFRs). The Kidney Disease Outcomes Quality Initiative guidelines recommend estimating GFRs with the Modification of Diet in Renal Disease (MDRD) or the Cockcroft-Gault equation. We examined the accuracy of the MDRD equation and creatinine clearance based on 24-hour urine collection to predict GFRs in a group of healthy donors.**

Materials and Methods: **We examined the medical records of 100 kidney donors who had undergone ^{99m}Tc-diethylenetriamine-pentaacetic acid (DTPA) renal clearance and creatinine clearance measurements at the transplant outpatient clinic of Cairo University Hospital in Cairo, Egypt, between June 2002 and July 2006. GFR was predicted with the abbreviated MDRD formula. We examined significant differences, potential correlations, and agreements between GFR as predicted and as measured.**

Results: **The mean $eGFR_{MDRD}$ was 8.16% lower than the ^{99m}Tc-DTPA GFR (116.11 ± 25.44 mL/min/1.73 m^2 vs 126.32 ± 24.21 mL/min/1.73 m^2; difference range, –84 to +61 mL/min/1.73 m^2; *P* = .002). Creatinine clearance was 13.14% higher than the ^{99m}Tc-DTPA GFR (142.90 ± 27.51 mL/min/1.73 m^2; difference range, +65 to –60 mL/min/1.73 m^2; *P* < .001). A significant positive correlation was observed when creatinine clearance and ^{99m}Tc-DTPA-measured GFR were compared (R=0.451; *P* = .000). No significant correlation was noted between $eGFR_{MDRD}$ and ^{99m}Tc-DTPA-measured GFRs (R=0.126; *P* = .211). A Bland-Altman analysis showed poor agreement between GFR_{MDRD} and creatinine clearance on the one hand and measured GFR on the other.**

Conclusions: **Neither the MDRD equation nor creatinine clearance is accurate in predicting GFRs in healthy donors.**

Key words: *Estimation of kidney function, Prediction equation, Creatinine clearance*

Introduction

An accurate estimation of the glomerular filtration rate (GFR) is essential in assessing prospective kidney donors. Inulin clearance and radioisotope studies are the most accurate means of measuring GFR, but they are cumbersome and expensive (1). The new Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines recommend estimating GFR by using the Modification of Diet in Renal Disease (MDRD) or the Cockcroft-Gaul equation (2). The MDRD equation was derived from 1628 subjects with chronic renal insufficiency enrolled in the MDRD study (3). The original MDRD formula used 6 variables (serum creatinine, albumin, urea nitrogen, sex, age, and ethnicity); a simpler equation requiring 4 variables (serum creatinine, sex, age, and ethnicity) that offered similar performance was proposed (4).

Owing to the demographically sensitive nature of the creatinine measurement, GFR prediction equations cannot always be applied to individual patient groups without validation (5). The MDRD equation has been evaluated in blacks with chronic kidney disease (6), scleroderma patients (7), patients with kidney disease

From the Departments of [1]Internal Medicine and [2]Medical Biochemistry, Faculty of Medicine, Cairo University, Cairo, Egypt

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Address reprint requests to: *Salwa Ibrahim, MD MRCP, Cairo University, Egypt, 3 Refaah Street, Flat 14, Dokki, Giza, Egypt 12311*
Phone: *0020122380307* ***E-mail:*** *salwaibrahim@hotmail.com*

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and normal serum creatinine levels (8), and in 46 normal individuals and 46 individuals with type 1 diabetes without evidence of nephropathy (9).

Several studies have been done to validate the use of MDRD formulae to assess GFRs for potential kidney donors and have shown mixed results (10-13). The MDRD equation underestimated measured GFRs in Swedish and American healthy donors (10-12). In an Indian study, the MDRD equation was more precise and accurate in estimating the GFR compared with the Cockcroft-Gault formula; however, both equations had a poor correlation with the measured GFR (13).

The purpose of this study was to assess the accuracy of the modified MDRD formula and creatinine clearance (CrCl) in evaluating renal function in kidney donors with regard to the radioisotope GFR.

Materials and Methods

We reviewed the medical records of 100 healthy kidney donors who had undergone measurements of ^{99m}Tc-diethylenetriamine-pentaacetic acid (DTPA) renal clearance and CrCl as part of a routine work-up at the transplant outpatient clinic at the Cairo University Hospital in Cairo, Egypt, between June 2002 and July 2006. The patients were hydrated orally or intravenously at 10 mL/kg per hour for 30 minutes before the start of the study. ^{99m}Tc- DTPA dosed at 50 μCi/kg was injected intravenously, and blood was sampled at 120, 180, 240 minutes after the injections. Three GFR measurements were averaged and standardized for body surface area of 1.73 m^2. Creatinine clearance was assessed based on serum creatinine level, 24-hour urinary creatinine, and volume and was adjusted to a body surface area of 1.73 m^2 (14, 15). Age, sex, and serum creatinine levels were recorded for the study subjects to estimate the GFR using the abbreviated MDRD formula (4, 16, 17): $GFR_{MDRD} = 186 \times [\text{serum creatinine}]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ (if female)}]$. The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki Principles.

Statistical analyses

Results are expressed as means ± SD. The *t* test was used to assess any statistically significant difference between the GFR measured by radionuclide method on one hand and the MDRD-predicted GFR and the CrCl on the other hand. The Pearson product moment correlation analysis was used to estimate the correlation between the results of GFR_{MDRD}, CrCL, and ^{99m}Tc-DTPA GFRs. Bias was defined by the mean prediction error (the sum differences between predicted and measured value divided by sample size). The R^2 statistics were derived by simple linear regression and reflect the predictive ability of the mode (precision). Accuracy of the predicted GFR and CrCl was described from the percentage of GFR values falling within 30% and 50% of the ^{99m}Tc-DTPA GFR. Statistical analyses of the Bland-Altman analysis were used to study agreement among the different methods of assessing the GFR. The limits of agreement were given by the means ± 1.96 SD. Values for *P* less than .05 were considered statistically significant. The data were analyzed using SPSS software (Statistical Product and Services Solutions, version 11.0, SPSS Inc, Chicago, IL, USA).

Results

Table 1 shows the main characteristics of the study group. There were 61 men and 39 women (mean age, 32.22 ± 7.23 years; range, 20-50 years). Body mass index ranged from 21.9 to 32.6 kg/m^2, and body surface area was 1.5 to 2.4 m^2. The mean $eGFR_{MDRD}$ was 8.16% lower than the mean ^{99m}Tc-DTPA GFR (116.11 ± 25.44 mL/min/1.73 m^2 vs 126.32 ± 24.21 mL/min/1.73 m^2, mean difference was –10.31 ± 4.59 mL/min/1.73 m^2; range, –84 to + 61 mL/min/1.73 m^2; $P = .002$) (Figure 1). Creatinine clearance was 13.14% higher than ^{99m}Tc-DTPA GFR (142.90 ± 27.51 mL/min 1.73 m^2; mean difference, 16.60 ± 27.26 mL/min/1.73 m^2; range + 65 to –60 mL/min/1.73 m^2; $P < .001$) (Figure 1).

Table 1. General and biochemical data of the study subjects.

Parameter	Mean ± SD	Range
Age (year)	32.22 ± 7.23	20-50
Sex (M/F)	61/39	-
Body mass index (kg/m^2)	28.31 ± 5.34	21.9-32.6
Body surface area (m^2)	1.82 ± 0.21	1.5-2.4
Serum creatinine (μmol/L)	67.18 ± 44.2	40.66-106.08
Blood urea nitrogen (mmol/L)	3.5 ± 0.98	3.4-4.6
Serum albumin (g/L)	45 ± 6.4	35-52
^{99m}Tc-DTPA GFR (mL/min/1.73 m^2)	126.32 ± 24.21	92.5-211
Adjusted CrCL (mL/min/1.73 m^2)	142.90 ± 27.51	70-178
MDRD GFR (abbreviated) (mL/min/1.73 m^2)	116.11 ± 25.44	60-179

Table 2 (data) and Figure 2 (graph) show the correlations of the studied methods. A significant positive correlation was observed when CrCl and measured GFR were compared ($R = 0.451$, $R^2 = 0.203$; $P = .000$). There was no significant correlation between

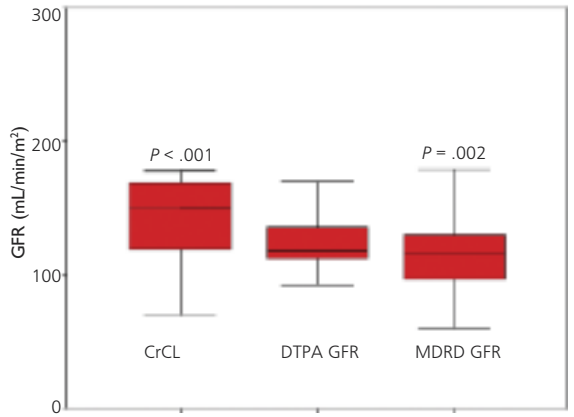

Figure 1. Mean DTPA-measured GFR in comparison with MDRD-predicted GFR and CrCl (mean ± SD).

Table 2. Analysis of MDRD eGFR and CrCL in comparison with DTPA-measured GFR; bias, precision, Pearson's correlation coefficient, concordance coefficient, and accuracy of GFR prediction.

	Bias	Precision R^2	Pearson correlation	Accuracy 30%	Accuracy 50%
MDRD	-10.31	0.016	0.126	48%	57%
CrCL	16.60	0.203	0.451*	20%	27%

(*$P < .05$)

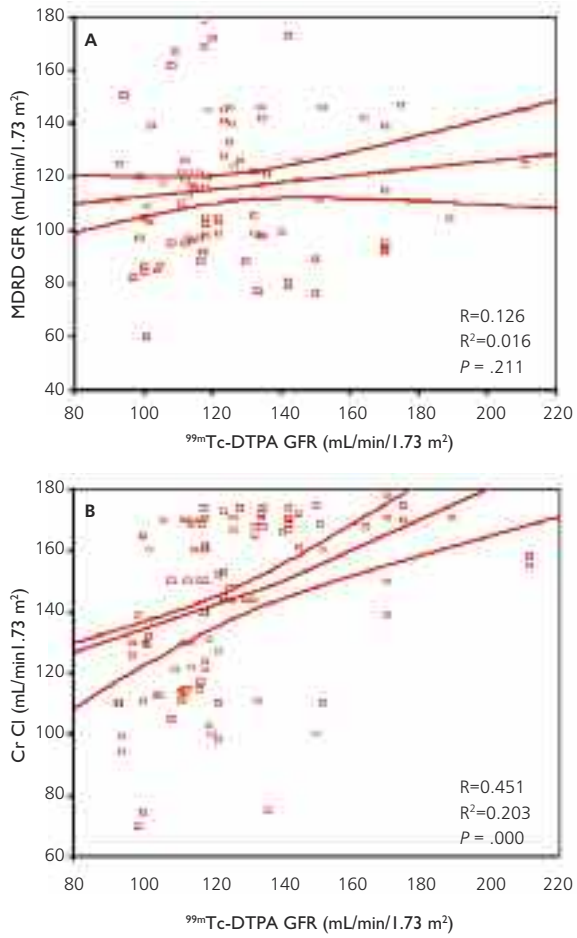

Figure 2. Linear regression analysis between isotopic and MDRD estimated GFR (A) and Cr Cl (B).

$eGFR_{MDRD}$ and measured GFR on the one hand (R=0.126, R^2=0.016; P = .211) and CrCl on the other hand (R=130, R^2=0.017; P = .98). Linear regression analyses showed that at $eGFR_{MDRD}$, less than 99.37 mL/min/1.73 m², $eGFR_{MDRD}$ underestimated the DTPA GFR values.

The concordance analysis (Table 2) revealed that $eGFR_{MDRD}$ was less biased (–10.31) and more precise and accurate compared with CrCl, as 48% of the predicted values were within 30%, and 57% of the values were within 50% of the DTPA-measured GFR. Creatinine clearance on the other hand showed a higher mean prediction error (16.60), with only 20% of donors within 30%, and 27% within 50% of the DTPA-measured GFR. A Bland-Altman analysis (Figure 3) was used to plot the distribution of the data with the limits of the mean ± 1.96 SD. The MDRD predicted equation underestimated measured the DTPA GFR in 62% of cases, whereas CrCl overestimated it in 78% of cases.

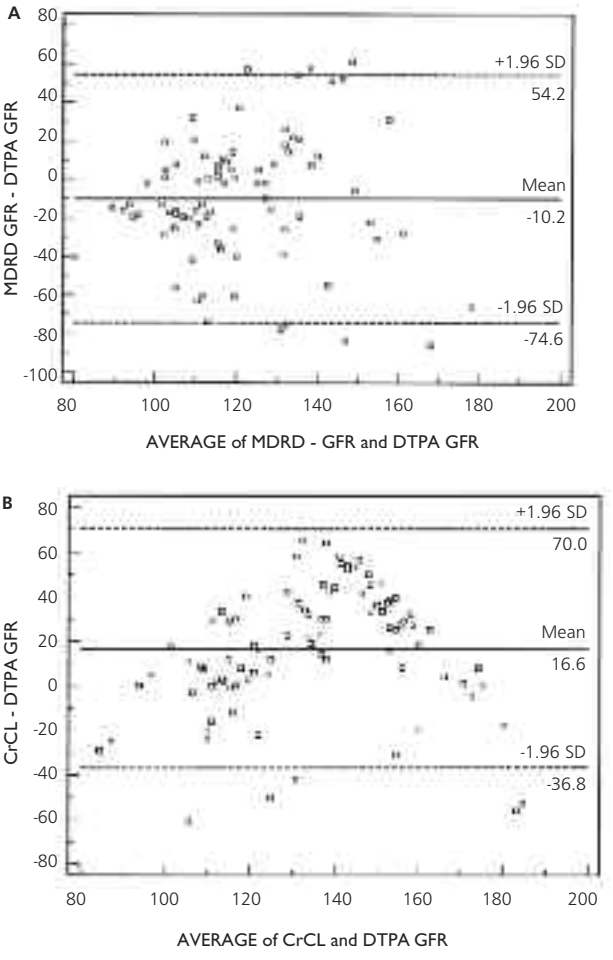

Figure 3. Bland-Altman analysis of agreement between isotopic GFR and MDRD-estimated GFR (A) and adjusted creatinine clearance level (B).

Discussion

The results of this study show that neither the MDRD equation nor CrCl accurately estimated GFRs in Egyptian kidney donors. A Bland-Altman analysis showed poor agreement between $eGFR_{MDRD}$ and CrCL on one hand and the measured GFR on the other hand (+54.2/–74.6 and +70/–36.8, respectively). Creatinine clearance, however, correlated better with the measured GFR compared with the $eGFR_{MDRD}$ (P = .000 and P = .211, respectively). The MDRD equation and CrCl demonstrated poor accuracy as assessed by values falling within 30% and 50% of the measured GFR (Table 2).

The results of this study agree with those of previous reports of poor performance of the MDRD equation in predicting GFRs in healthy kidney donors (10-13). A recent Swedish study showed poor correlation between iohexol clearance and the GFR_{MDRD} (R^2=0.045) in kidney donors (10). Similarly, the MDRD equation underestimated iohexol GFR by 6.45 ± 9.5 mL/min and was within 10% of the actual GFR in only half of an examined group of American healthy donors (11). The MDRD equation significantly underestimated the measured GFR with a bias that is similar to our results (9 mL/min/1.73 m^2) in a study of 457 potential kidney donors (12). A study of a group of Indian donors showed a poor correlation and a high error level in predicting GFR using the MDRD and Cockcroft-Gault formulas and CrCL, but GFR_{MDRD} was more precise and accurate (76% within 30%) compared with CrCl (69% within 30%) (13). The median percentage absolute difference between calculated and measured GFR was 20.8 and 25.5 for the simplified MDRD equation and CrCl, respectively (13).

Others have shown a higher difference (29%) between the measured and MDRD predicted GFR, thus invalidating its use in healthy donors (18). Lin and coworkers reported a mean difference of 28.7 mL/min between simplified MDRD eGFR and DTPA-measured GFR (1). Of note, our study demonstrated much lower accuracy rates for both the GFR_{MDRD} and CrCl compared with the study by Mahajan and associates (13) (76% and 69% within 30% of measured GFR, respectively) and Lin and associates (1) (65% and 95% accuracy within 30% and 50% for GFR_{MDRD}).

The poor performance of the MDRD equation in predicting GFR in our study could be explained by the fact that the MDRD equation was derived from American patients with moderate to severe kidney disease in the MDRD study (3). The equation has been validated in different studies for use in chronic kidney disease patients (19-20) but not in healthy individuals from different ethnic backgrounds (1, 10-13, 18). Serum creatinine measurements in our laboratory were not calibrated to match those of the MDRD laboratory. Lack of calibration of the serum creatinine measurement method might affect precision and accuracy of the MDRD equation and CrCl, especially when estimating GFR in subjects with normal or mildly impaired renal function, as small changes in serum creatinine result in large changes in calculated CrCL and estimated GFR (3). Nevertheless, we have used the MDRD formula suggested by the National Kidney Disease Education Program for predicting the GFR when the serum creatinine measurement method is not calibrated to be traceable to isotope dilution mass spectrometry (16-17).

It is noteworthy that the MDRD eGFR underestimated the measured GFR at a level below 99.37 mL/min/1.73 m^2 in the present study. Four donors in the present study (4%) had an estimated $eGFR_{MDRD}$ below 80 mL/min/1.73 m^2, which is the lowest GFR acceptable for donation. This means that using MDRD formulae to predict GFR in healthy donors as well as in the general population should be interpreted with caution, taking into consideration other risk factors and markers of chronic kidney disease to avoid improper diagnosis of renal insufficiency in healthy subjects.

Creatinine clearance based on 24-hour urine collection significantly overestimated the GFR in our study, despite standardization of body surface area. However, there was a significant correlation between CrCL and DTPA when measuring GFR in our study (R=0.451). The lack of accuracy of CrCl to predict the GFR in our study is not surprising because of the reported inaccuracies of using 24-hour urine collections to measure CrCl resulting from under/overcollection of urine and tubular creatinine secretion (21-22). Bertolatus and associates (21) found that 10% of healthy donors had lower CrCl levels compared with the measured GFR. Coresh and associates (22) concluded that there is no advantage in 24-hour urine collection over Cockcroft-Gault estimation when compared with a GFR determined by radionuclide methods.

In conclusion, our results show that neither the abbreviated MDRD equation nor CrCl accurately

predict GFRs in healthy donors as determined by the radioisotope method. To avoid the risk of underestimating kidney function in individuals without chronic kidney disease, care should be taken in interpreting the results of MDRD-derived GFR in healthy individuals, especially when the eGFR is less than 99 mL/min/1.73m^2.

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