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Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: http://www.tandfonline.com/loi/irnf20

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To cite this article: Amin R. Soliman, Ahmed Fathy, Sahier Khashab & Noha Shaheen (2013) Comparison of Abbreviated Modification of Diet in Renal Disease Formula (aMDRD) and the Cockroft–Gault Adjusted for Body Surface (aCG) Equations in Stable Renal Transplant Patients and Living Kidney Donors, Renal Failure, 35:1, 94-97, DOI: 10.3109/0886022X.2012.731970

To link to this article: http://dx.doi.org/10.3109/0886022X.2012.731970

Published online: 27 Nov 2012.

Renal Failure, 2013; 35(1): 94–97

ISSN 0886-022X print/1525-6049 online
DOI: 10.3109/0886022X.2012.731970

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healthcare

CLINICAL STUDY

Comparison of Abbreviated Modification of Diet in Renal Disease Formula (aMDRD) and the Cockroft–Gault Adjusted for Body Surface (aCG) Equations in Stable Renal Transplant Patients and Living Kidney Donors

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Abstract

The performance of abbreviated Modification of Diet in Renal Disease formula (aMDRD) and the Cockroft–Gault adjusted for body surface (aCG) equations as compared with measured ^{125}I-iothalamate glomerular filtration rate was analyzed in patients with stable renal transplantation (RTx) and in potential living kidney donors (LKD). One hundred and thirty-one patients had RTx and 150 were LKD. The paired *t*-test showed that the estimated glomerular filtration rate (GFR) values through the aMDRD and the corrected CG equations were significantly different from each other ($p < 0.01$). There were significant differences between GFRs estimated using aCG and aMDRD equations ($p < 0.001$) in both groups (RTx and LKD) of different ages. The Pearson correlation coefficient between aCG and aMDRD equations was good (0.77, $p < 0.01$), but the kappa coefficient was 0.39, indicating a low agreement between the two formulae. In RTx patients with GFR <60 mL/min/1.73 m^2, the aMDRD equation performed better than the aCG formula with respect to bias (–0.6 vs. 3.0 mL/min/1.73 m^2, respectively) and accuracy within 30% (72% vs. 56%, respectively) and 50% (91% vs. 73%, respectively). Similar results are reported for 48 diabetic RTx patients. In the LKD, the aMDRD equation significantly underestimated the measured GFR when compared with the aCG formula, with a bias of –8.0 versus 2.2 mL/min/1.73 m^2, respectively ($p < 0.05$). We can conclude that the Cockroft and MDRD equations cannot be used interchangeably in clinical transplantation practice and in order to adjust drug doses.

Keywords: living donors, renal transplantation, MDRD, survival, Cockroft–Gault

INTRODUCTION

Patients with end-stage renal disease have two options for treatment: dialysis or transplant. Those opting for a transplant must then decide whether to have a living donor transplant (if there is a suitable donor) or to go on the waiting list for a cadaver kidney. However, a living donor transplant does have the potentially negative long-term consequences of living with a single kidney. Thus far, numerous studies (follow-up of 20 years) of living donors have noted no evidence of long-term deterioration of the remaining kidney's function and glomerular filtration rate (GFR).[1]

The limitations of serum creatinine and urinary creatinine clearance for the estimation of estimated GFR are well known. Serum creatinine concentration is affected by the GFR but is also affected by several factors that are independent of GFR, such as age, race, muscle mass, gender, medication use, and catabolic state.[2–6] Moreover, different laboratories measure serum creatinine using different methods, giving results that are difficult to compare. The measurement of urinary creatinine clearance overcomes some of the limitations of serum creatinine but remains inaccurate because of collection errors and changes in creatinine excretion. Various creatinine-based equations have been developed in an attempt to improve the estimation of GFR from serum creatinine.[6] These equations, however, have not been shown to be accurate in renal transplant recipients and their suitability in clinical trials has been called into question.[7]

With the increasing incidence of kidney dysfunction, the use of formulas to estimate kidney function is implemented more frequently in clinical practice.[8] The most frequently used formulas are the Cockcroft–Gault and

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Received 11 August 2012; Revised 29 August 2012; Accepted 9 September 2012

(abbreviated) Modification of Diet in Renal Disease (aMDRD) equations. The Cockcroft–Gault equation estimates clearance of creatinine, whereas the MDRD estimates GFR.[9,10] At present, for subgroups of people who are old, underweight, or overweight, no clear-cut advice exists regarding which formula is best used for optimal estimation of kidney function. Both Cockcroft–Gault and aMDRD have been compared in the same population against a gold standard method for estimating GFR. These studies show conflicting results because of different study populations, different gold standard GFR measurements, and differences in creatinine assay calibration.[11] Furthermore, the recently developed Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula has not been validated yet, outside the original publication; therefore, a pragmatic study to evaluate the most often used formulas, in a study population in which a GFR measurement is requested, is needed.[12] Furthermore, these formulas need to be compared with an excellent gold standard GFR measurement. GFR measured by continuous infusion of ^{125}I-iothalamate can be considered as the gold standard in the absence of bladder catheterization.[13] ^{131}I-hippuran is added to correct for inaccurate urine collections without using a bladder catheter to optimize GFR measurement further.[13–17]

The purpose of this study was to determine the concordance between two equations used for estimating GFR in order to verify the possibility to be used interchangeably in renal transplant practice.

PATIENTS AND METHODS

The performance of aMDRD and the Cockroft–Gault adjusted for body surface (aCG) equations as compared with measured ^{125}I-iothalamate GFR (iGFR) was analyzed in patients with stable renal transplantation (RTx) and in potential living kidney donors (LKD). All RTx and LKD in outpatient sitting ($n = 281$) who underwent an iGFR between January 2008 and December 2010 were retrospectively considered for analysis. Of these, 131 patients had RTx and 150 were LKD. All LKD underwent ^{125}I-iothalamate renal clearance study as part of a routine work-up for potential kidney donation. On chart review, all 150 potential donors had sufficient clinical and laboratory data to estimate GFR, including age, gender, weight, height, and serum creatinine. Donors who underwent ^{125}I-iothalamate studies were asked to fast for at least 8 h and given a water load of 10 mL/kg and five drops of potassium iodide diluted in 15 mL of water orally (to block thyroid uptake of ^{125}I-iothalamate) at the initiation of the study. Thirty-five microcuries of ^{125}I-iothalamate was injected subcutaneously into the upper arm. Blood was drawn and urine was sampled at time 0 (before ^{125}I-iothalamate injection) and at 60, 120, and 180 min. Total urine volume and urinary flow rates were assessed every 60 min. Oral fluid hydration was administered at 500 mL/h as tolerated. GFR measurements for two timed urine collections were averaged and standardized for a body surface area (BSA) of 1.73 m^2. The reference normal values for serum creatinine were 0.8–1.5 mg/dL in men and 0.8–1.3 mg/dL in women. The BSA was calculated according to Du Bois and Du Bois: BSA = [body weight$^{0.425}$ (in kilograms) × height$^{0.725}$ (in centimeters)] × 0.007184.

The prediction equations that we used are listed as follows:

Cockcroft–Gault (CG): Cockcroft and Gault, 1976

$$\mathrm{CrCl} \times \mathrm{BSA}/1.73\mathrm{m}^2$$

a. For men: $\mathrm{CrCl} = [(140 - \mathrm{age}) \times \mathrm{weight(kg)}]/\mathrm{SCr} \times 72$

b. For women: $\mathrm{CrCl} = \{[(140 - \mathrm{age}) \times \mathrm{weight(kg)}]/\mathrm{SCr} \times 72\} \times 0.85$

MDRD 2: Levey et al., 2000

$$\mathrm{GFR} = 186 \times [\mathrm{SCr}]^{-1.154} \times [\mathrm{age}]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.212 \text{ if patient is black}]$$

a. For men: $\mathrm{weight} \times [29.3 - (0.203 \times \mathrm{age})] \times [1 - (0.03 \times \mathrm{SCr})]$ $(14.4 \times \mathrm{SCr}) \times (70/\mathrm{weight})$

b. For women: $\mathrm{weight} \times [25.3 - (0.175 \times \mathrm{age})] \times [1 - (0.03 \times \mathrm{SCr})]$ $(14.4 \times \mathrm{SCr}) \times (70/\mathrm{weight})$

^{125}I-iothalamate GFR measurement was done yearly in all renal transplant recipients as per protocol follow-up. Estimation of the GFR by the formula was usually done at the same time of ^{125}I-iothalamate GFR measurement as a prerequisite before any scintigraphy.

Statistical Analysis

Fisher's exact test was used for proportions and *t*-test for comparison of means. A Pearson correlation coefficient was also calculated for the normally distributed GFR data (Shapiro–Wilk test for normality, $p = 0.98$). The mean and median absolute differences were calculated from absolute difference = predicted value − measured value. The percentage absolute difference was calculated as percentage absolute difference = predicted value − measured value × 100 measured value. SAS for Windows version 8.0 (SAS Institute Inc., Cary, NC, USA) was used for all statistical calculations.

RESULTS

Table 1 shows basic subjects' characteristics with both kidney donors and renal transplant patients compared together. On the other hand, Table 2 shows GFR by different calculations in both kidney donors and patients

Table 1. Subjects' characteristics.

Parameter	Kidney donors	Renal transplant
Sample size	131	150
Age (years)	41 ± 10 (21–58)	40 ± 11 (18–60)
Male gender	102 (78%)	89 (59.3%)
Weight (kg)	73.5 ± 13.8 (49.3–104.2)	79.1 ± 14.3 (49.5–110.2)
Height (cm)	166.6 ± 10.2 (151.8–187.6)	169.0 ± 10.1 (150.4–188.0)
BSA (m^2)	1.88 ± 0.3 (1.5–2.3)	1.86 ± 0.3 (1.5–2.4)
Serum creatinine (mg/dL)	0.9 ± 0.15 (0.7–1.2)	1.6 ± 0.4 (0.7–2.2)
Serum urea nitrogen (mg/dL)	12 ± 5 (7–26)	21 ± 5 (11–31)
Albumin (g/dL)	4.2 ± 0.3 (3.5–5.2)	4.0 ± 0.3 (3.4–5.0)

Note: BSA, body surface area.

Table 2. GFR by different calculations in both kidney donors and patients with stable renal transplantation.

GFR method	Mean (SD)	Minimum	Maximum
GFR aMDRD[a]			
Kidney donors[b]	85.7 (30.4)	79.8	138.2
Patients with stable renal transplantation[b]	61.5 (22.8)	18.7	123.5
GFR CG[a]			
Kidney donors[b]	98.5 (30.6)	75.8	135
Patients with stable renal transplantation[b]	77.6 (24.5)	15.5	132.7
GFR isotope			
Kidney donors	89.5 (17.8)	78.1	145.6
Patients with stable renal transplantation	59.8 (26.7)	14.5	144.4

Notes: CG, Cockroft–Gault; aMDRD, abbreviated Modification of Diet in Renal Disease; SD, standard deviation; GFR, glomerular filtration rate.
[a]aMDRD versus corrected CG equations in the same group, $p < 0.01$.
[b]Comparison of aMDRD versus corrected CG equations in different groups, $p < 0.001$.

with stable renal transplantation. The paired *t*-test showed that the estimated GFR values through the aMDRD and the corrected CG equations were significantly different from each other ($p < 0.01$). There were significant differences between GFRs estimated using aCG and aMDRD equations ($p < 0.001$) in both groups (RTx and LKD) of different ages. The Pearson correlation coefficient between aCG and aMDRD equations was good (0.77, $p < 0.01$), but the kappa coefficient was 0.39, indicating a low agreement between the two formulae. In RTx patients with GFR <60 mL/min/1.73 m^2, the aMDRD equation performed better than the aCG formula with respect to bias (–0.6 vs. 3.0 mL/min/1.73 m^2, respectively) and accuracy within 30% (72% vs. 56%, respectively) and 50% (91% vs. 73%, respectively). Similar results are reported for 48 diabetic RTx patients. In the LKD, the aMDRD equation significantly underestimated the measured GFR when compared with the aCG formula, with a bias of –8.0 versus 2.2 mL/min/ 1.73 m^2, respectively ($p < 0.05$).

DISCUSSION

Our work showed that in the LKD, the aMDRD equation significantly underestimated the measured GFR when compared with the aCG formula. Moreover, there were significant differences between GFRs estimated using aCG and aMDRD equations in RTx and LKD of different ages.

All potential kidney donors should have GFR estimated. Creatinine-based methods may be used to estimate the GFR; however, creatinine clearance (as calculated from 24-h urine collections) may underestimate or overestimate GFR in patients with normal or near-normal renal function.[18] The calculated GFR values (MDRD, Cockcroft–Gault) are not standardized in this population and may overestimate GFR. These methods may be replaced or supplemented by isotopic estimation of GFR (e.g., iothalamate, 99-technetium clearances) in cases of borderline GFR determination.[19-21] In a report of the Amsterdam Forum on the care of the live kidney donor, Jaime Herrera-Acosta noted that some might have difficulty in obtaining ^{125}I-iothalamate clearances, for which his center substitutes creatinine clearances obtained during mild water diuresis and short-term urine collections to make sure that urine flows are exact.[22] An excellent correlation of creatinine clearance with simultaneous ^{125}I-iothalamate clearance was achieved in 46 kidney donors ($r = 0.84$, $p < 0.0001$).

A strong feature of our study is that we were able to compare both the two most frequently used and the newest equations to estimate kidney function in both LKD and stable renal transplant recipients against an excellent gold standard method to measure GFR. We were able to

study the influence of measured GFR, gender, age, body weight, and BMI on the performance of the formulas by stratification on these parameters.[23-24]

We can conclude that the Cockroft and MDRD equations cannot be used interchangeably in clinical transplantation practice and in order to adjust drug doses. The present data add validation to the aMDRD equation in patients with RTx, especially those with diabetes but suggest that its use is problematic in healthy donors.

***Declaration of interest*:** The authors report no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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