

COMPARISON BETWEEN COCKROFT-GAULT AND MDRD FORMULA FOR THE ESTIMATION OF GLOMERULAR FILTRATION RATE IN CHRONIC KIDNEY DISEASE PATIENTS

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Abstract

The purpose of this study was to determine the concordance between two equations used for estimating glomerular filtration rate, in order to verify the possibility to be used interchangeably in the clinical practice. We present a retrospective study performed on a group of 258 patients with chronic kidney disease treated between January 2008 and December 2009 in the Department of Nephrology of The County Hospital Targu Mures, Romania. For every patient, glomerular filtration rate (GFR) was estimated with Cockcroft-Gault (aCG) equation adjusted for body surface (aCG) and abbreviated Modification of Diet in Renal Disease (MDRD) formula (aMDRD). The paired t-test showed that the estimated GFR through the abbreviated MDRD and the corrected CG equations were significantly different from each other ($p < 0.0001$). There were significant differences between glomerular filtration rate estimated with aCG and aMDRD equations ($p < 0.0001$) between groups of patients of different ages: 41-50 years, 51-60 years and 61-70 years, but not in patients under 40 years and over 70 years. 49.22% of the patients with $GFR < 60 \text{ mL/min/1.73 m}^2$ using the aCG equation are included in the same GFR interval in MDRD, and only 8.91% of patients had an estimated $GFR \geq 60 \text{ mL/min/1.73 m}^2$ with both formulae. The Pearson correlation coefficient between the aCG and the MDRD equations was good (0.83, $p < 0.0001$), but the kappa coefficient was 0.48, indicating a low agreement between the 2 formulae. The conclusion of this study is that the Cockcroft and MDRD equations cannot be used interchangeably in clinical practice in order to adjust drug doses.

Rezumat

Studiul de față și-a propus compararea a două ecuații de calcul ale ratei de filtrare glomerulară pentru a verifica dacă acestea pot fi folosite interschimbabil în practica medicală. Studiul a fost realizat retrospectiv, pe un grup de 258 pacienți diagnosticați cu boală renală cronică internați în Departamentul de Nefrologie a Spitalului Clinic Târgu-Mureș, România. Pentru fiecare pacient estimarea ratei de filtrare glomerulară (RFG) a fost realizată folosind ecuația *Cockcroft-Gault* corectată pentru suprafața corporală și ecuația *Modification of Diet in Renal Disease* (MDRD) cu patru variabile. Compararea rezultatelor obținute cu ajutorul celor două formule reliefează existența unei diferențe statistic semnificative ($p < 0,0001$) atât pentru întregul lot de pacienți, cât și pentru grupele de vârstă 41-50 ani, 51-60 ani, 61-70 ani. 49,22% din pacienții cu $RFG < 60 \text{ mL/min/1,73 m}^2$ estimată pe baza ecuației *Cockcroft-Gault* au fost încadrați în același interval și de formula MDRD. 8,91% dintre pacienți au avut o $RFG \geq 60$

mL/min/1.73 m² calculată cu ajutorul ambelor formule. Coeficientul de corelație Pearson între cele două formule a fost 0,83, $p < 0,0001$, dar indicele kappa a fost 0,48, indicând o concordanță mică între formule. În concluzie, ecuațiile *Cockcroft Gault* și *Modification of Diet in Renal Disease* nu pot fi utilizate interschimbabil în clinică.

Keywords: glomerular filtration rate, Cockcroft Gault equation, Modification of Diet in Renal Disease (MDRD) equation

Introduction

Glomerular filtration rate (GFR) is an important tool for kidney evaluation, in order to detect the early impairment of renal function, to allow correct dosage of drugs cleared by the kidneys or to evaluate patients before transplantation or before using potentially nephrotoxic radiographic contrast media.

For clinical application, the assessment of renal function needs to be accurate, inexpensive and easy to apply. For this reason, in an attempt to find the best method to calculate GFR, a variety of formulas have been developed.

The National Kidney Foundation Dialysis Outcome Quality Initiative (K/DOQI) and European Best Practice Guidelines recommend the use of prediction equations to estimate the GFR from serum creatinine (SCr) [19]. Unfortunately, no single method is ideal for all patients because creatinine is modified by many factors: proximal tubular secretion and extrarenal elimination of SCr, gender and body size related differences, ethnic differences, critical illness, dietary intake and serum creatinine assay variance [2,6,22,24].

In adults, the most commonly used formulae are those derived from the Modification of Diet in Renal Disease (MDRD) and the Cockcroft and Gault equations [15].

There is much controversy about which method is best for a particular patient group. The purpose of this study was to determine the concordance between the two equations used for estimating glomerular filtration rate, in order to verify the possibility to be used interchangeably in clinical practice.

Materials and Methods

Study population

This is a retrospective study made on a group of patients with chronic kidney disease treated between January 2008 and December 2009 in the Department of Nephrology of The County Hospital Targu-Mures, Romania. Data on age, sex, body weight, serum creatinine and about the cause of chronic kidney disease were collected from the observation sheets. Patients with incomplete data, who had unstable renal function or who needed kidney replacement therapy were excluded from the study. Two hundred and fifty

eight individuals were included in the study. For every patient, GFR was estimated with Cockcroft-Gault (CG) and abbreviated MDRD formula (aMDRD) [7].

The MDRD Study equation estimates GFR adjusted for body surface area (BSA). In order to compare the CG and MDRD equations we had to use the adjusted Cockcroft-Gault (aCG) formula (adjusted for BSA) [9].

Formulas used to calculate glomerular filtration rate were:

-adjusted Cockcroft-Gault: $(140 - \text{Age}) \times \text{weight (kg)} \times 0.85 \text{ (if female)} \times 1.73 / 72 \times \text{SCr} \times \text{BSA}$, where $\text{BSA (m}^2\text{)} = \text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 0.007184$, according to Du Bois formula [9]

-abbreviated MDRD: $\text{eGFR} = 186 \times \text{SCr}^{-1.154} \times \text{Age}^{-0.203} \times 1.210 \text{ (if black)} \times 0.742 \text{ (if female)}$ [16]

Patients were classified in five subgroups defined by eGFR :

- above 90 mL/min/1.73 m²,
- between 60 and 90 mL/min/1.73 m²,
- 30-60 mL/min/1.73 m²,
- 15-30 mL/min/1.73 m²,
- below 15 mL/min/1.73 m² [26].

Statistical analysis

The results are presented as mean $\pm$ standard deviation (SD). Statistical analysis was performed with paired Student's t-test. The correlation between methods was performed through the Pearson's correlation coefficient. Agreement was determined using kappa statistics and Bland-Altman plot [3,18].

Statistical analysis was performed using the statistical software GraphPad Prism 5. All p values less than 0.05 were considered to be significant.

Results and Discussion

The study group comprised 258 caucasian individuals (131 male, 127 female), aged between 21 to 86 years (mean age 57.5 ± 13.3 years). The mean serum creatinine level was 3.05 ± 2.51 mg/dL (range 1.32 – 3.86 mg/dL); mean level of blood urea nitrogen was 103.68 ± 68.64 mg/dL (range 54.50 – 133.22 mg/dL). Anthropometric, clinical and biological characteristics of the study population are presented in table I. Table II shows the distribution of patients by age and differences between the two equations (aCG and aMDRD). The mean estimated GFR was 47.7 ± 32.3 mL/min/1.73 m² using the aCG formula, and 35.7 ± 25.5 mL/min/1.73 m² using the aMDRD formula.

Table I
Anthropometric, clinical and biological characteristics of the study population

	Total	Females	Males	p
Age (years)	57.5 ± 13.3	55.9 ± 13.7	59.2 ± 12.7	0.06
Creatinine (mg/dL)	3.05 ± 2.51	3.51 ± 2.71	2.60 ± 2.22	0.00
eGFR – aCG	47.7 ± 32.3	48.0 ± 34.0	46.8 ± 30.8	0.00
eGFR – aMDRD	35.7 ± 25.5	38.4 ± 27.8	33.0 ± 23.2	0.00
Diabetes (no)	68	32	36	0.78
Body surface	1.85 ± 0.227	1.75 ± 0.194	1.97 ± 0.203	0.00
Body mass index	28.14 ± 5.36	28.25 ± 5.74	28.02 ± 4.96	0.09
Weight (Kg)	77.93 ± 17.21	72.34 ± 16.13	83.70 ± 16.43	0.00

Table II
Comparison of aCG and aMDRD study equations for different age groups

	Females/Males (number)	eGFR with aCG – Median (25% - 75%)	eGFR with aMDRD - Median (25% - 75%)	p
21-30 years	9/5	26.82 (16.40 - 60.89)	18.57 (12.26 - 47.02)	0.15
31-40 years	11/5	37.26 (16.91 - 70.03)	24.42 (12.90 - 46.84)	0.08
41-50 years	15/16	40.51 (19.03 - 69.52)	25.31 (13.52 - 46.98)	<0.0001
51-60 years	47/44	46.78 (26.23 - 75.11)	31.94 (16.04 - 46.98)	<0.0001
61-70 years	29/28	43.42 (18.95 - 74.76)	28.38 (15.30 - 53.23)	<0.0001
Over 71 years	20/29	39.55 (23.69 - 56.40)	40.74 (20.42 - 58.07)	0.5114
Total	7.73/127	29.97 (15.16 - 51.50)	40.91 (20.41 - 69.72)	

The paired t-test showed that the estimated GFR using the abbreviated MDRD and the corrected CG equations were significantly different from each other ($p < 0.0001$). There were significant differences between glomerular filtration rates estimated with aCG and aMDRD equations ($p < 0.0001$) in the groups of patients of different age: 41-50 years, 51-60 years and 61-70 years, but not in patients under 40 years and over 70 years.

Assessment of GFR using aCG and aMDRD resulted in statistically significant differences both for women and for men.

Table III

Patient classification in the different intervals of eGFR values (mL/min/1.73 m²) estimated by the aCG and aMDRD equations

	aMDRD formula						
aCG formula		>90	[60-90)	[30-60)	[15-30)	<15	Total
	>90	7	16	8	0	0	31
	[60-90)	4	16	26	0	0	46
	[30-60)	0	4	43	33	4	84
	[15-30)	0	0	4	31	22	57
	<15	0	0	0	3	37	40
		11	36	81	67	63	258

The number of patients included in the different intervals of eGFR values estimated by aCG and aMDRD formula is shown in table III. A percent of 49.22% of the patients with eGFR < 60 mL/min/1.73 m² using the aCG equation are included in the same eGFR interval in aMDRD, and only 8.91% of patients had an estimated GFR ≥ 60 mL/min/1.73 m² with both formulae.

As it is shown in table III, aCG formula includes more patients in the group with eGFR higher than 60 mL/min/1.73 m² as compared to aMDRD formula (77 *versus* 47 patients, i.e. 29.85% *versus* 17.05%), whereas the aMDRD equation includes a higher number of patients in the group with eGFR lower than 30 mL/min/1.73 m² as compared to the aCG formula (130 *versus* 97, i.e. 50.38% *versus* 37.59%).

When eGFR values were evaluated with either aCG and aMDRD, the patients were classified differently in 124 cases (48.06%).

Bland–Altman plots for the differences of aGFR-CG and aGFR-MDRD against the combined mean values are shown in figure 1.

The limits of agreement (mean difference ± 1.96 SD of difference) for aCG and aMDRD formulae ranged between –22.96 to 46.80 mL/min/1.73 m². Thus, the aMDRD estimation may range from –22.96 mL/min below to 46.80 mL/min above the aCG estimation for 95% of the cases. This dispersion of values agrees with the modest index of agreement between both equations.

The Pearson correlation coefficient between the aCG and the aMDRD equations was good (0.83, $p < 0.0001$), but the kappa index was 0.48, indicating a low agreement between the 2 formulae (Figure 1).

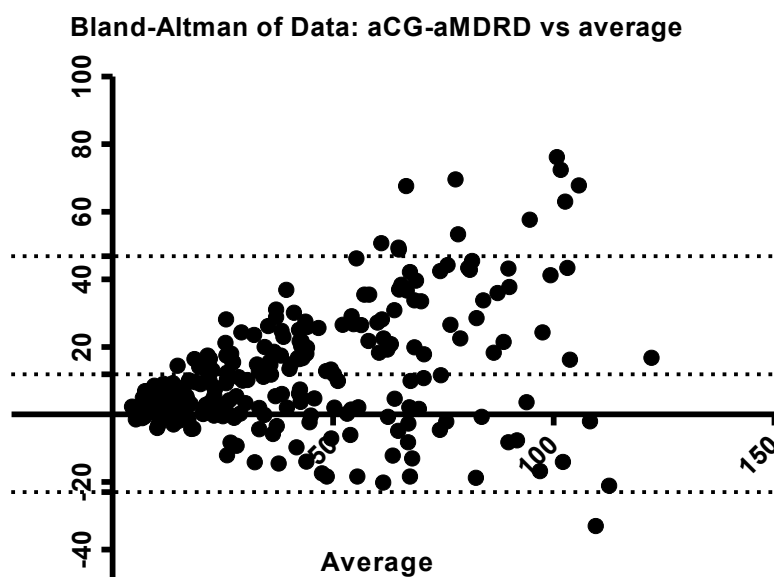


Figure 1.

Plot of differences in GFR values between the aCG and aMDRD formulas and mean values of the two formulae. The points in dotted line are 2 standard deviations distance above or below from the mean, bias = 11.91, 95% limits of agreement (from -22.96 to 46.80).

The glomerular filtration rate is very important in clinical practice, especially for a correct dosage of drugs with renal excretion. In the recent years, chronic kidney disease was recognized as a public health problem because it's increasing prevalence and the enormous financial burden [8]. In chronic kidney disease treatment, the dose-adjusting is a difficult task due to the particularities in drugs' clearance, modified absorption, distribution and metabolism. Drug-related problems are common in patients with altered kidney function [13].

In clinical practice, the assessment of GFR with high accuracy needs exogenous markers and is difficult to perform because invasive techniques and expensive equipment are needed.

Therefore, the mathematical estimation of GFR based on serum creatinine and some anthropometric factors such as gender, age and ethnicity is a useful method for evaluating kidney function.

Two formulae are widely used in the clinical practice: CG and MDRD. From it's application in practice, Cockcroft- Gault's formula became

the traditional method used to quantify renal function and for guiding dose adjustment. Because it has been shown that CG produces large overestimates of creatinine clearance due to creatinine secretion, and because it is well known that extreme values of weight (obese or cachectic), muscle mass, age, race [11,17,21] are associated with a much weaker correlation with the patient's renal function, we are trying nowadays to find other equations for the rapid assessment of renal function.

The Modification of Diet in Renal Disease (MDRD) Study equation is now considered as providing more accurate estimates of glomerular filtration rate (GFR) than the CG equation in patients with chronic kidney disease (CKD). Therefore MDRD equation is used to staging CKD, but little is known about how the equation should be used for drug dosage initiation and adjustment.

None of these formulas has been validated for calculating drug doses in patients with renal dysfunction. A great number of studies tried to establish the degree of correlation of the two equations and which can be more properly used for dose adjustments [5].

Our study compared abbreviated MDRD (aMDRD) with corrected CG (aCG) formula in a population with different degrees of chronic kidney disease and demonstrated that there are significant differences between glomerular filtration rate estimated with aCG and aMDRD equations ($p < 0.0001$) in patients of different age: 31-40 years, 41-50 years, 51-60 and 61-70 years.

Our data are consistent with other clinical studies highlighting the discrepancies between the two equations for estimating GFR.

In a study of 5504 patients, a third of them being African American and a similar number diagnosed with diabetes, Stevens et al. found a great discordance (11% to 29%) between aMDRD and aCG equations overall and in subgroups of patients. Even so, the authors considered that the MDRD Study equation can also be used for pharmacokinetic studies and drug dosage adjustments [23].

In an observational analysis of 409 patients with chronic kidney disease who were admitted to a tertiary care facility, Wargo et al. demonstrated statistically significant differences between the CG and MDRD equations, resulting in different dosing recommendations in 21-37% of the patients [25].

The differences between formulas were also reported by Froissart et al. in a group of 2095 European non-black individuals. The conclusion of the study was that both equations lack precision and that the percentage of

erroneous inclusion in various stages of chronic kidney disease was 30% [10].

Botev's study results are similar: approximately 60% of the population classified correctly in the five GFR groups defined by the Kidney Disease Outcomes Quality Initiative-Chronic Kidney Disease (K/DOQI-CKD) classification [4]. Although in the group under 30 years the number of patients was small enough to draw statistical conclusions, we found no statistically significant differences between aCG and aMDRD equations for age groups 21-30 and over 70 years.

Results from the literature on this subject are conflicting.

In the study of Alagiakrishnan on 170 elderly patients a 17% discordance rate (9.61 mL/min) and a low agreement was registered for the two formulae [1]. The study was conducted on elderly patients with chronic kidney disease, only 20% of the patients showing serum creatinine levels higher than normal.

In a group of 180 patients with a mean age of 85 years, of which 30% were Asian, Gill et al. found differences between mean MDRD-GFR and CG-GFR (72.9 mL/min/1.73 m² vs 52.1 mL/min/1.73 m²), with a rate of 37.2% of the patients categorized in the same stage of CKD by both methods. The authors concluded that CG and MDRD provided discordant estimations in over 60% of the elderly patients and that their interchangeable use cannot be advocated in the dosing of medications until further prospective validations should be performed [12].

Péquignot et al., in a study on 121 patients aged 70 or older, found a 50% misclassification rate according to MDRD and a 33% rate according to CG. They concluded that in elderly hospitalized patients CG gave a better prediction of measured creatinine clearance (CrCl) than MDRD [20].

In a review of 26 articles comparing CG and MDRD in terms of precision, accuracy and the risk of misclassifying by two CKD stages, Helou decided that CG was still the best formula for the elderly patients, so it may be early to replace CG by MDRD in drug studies [14].

It is quite possible that these results should be explained by patient's selection methods: different age groups, patients with or without chronic kidney disease, patients from acute care settings, hospitalized or not.

A possible explanation for the discrepancy between the formulas could be the percentage of diabetics: both the Cockcroft-Gault and the MDRD equations were developed primarily in non-diabetics, thereby raising questions regarding their use in patients with *diabetes mellitus*. Also, different anthropometric characteristics of the patients may be responsible

for the results of different studies, as well as the presence of calibration of the creatinine assay.

Based on this study, the two equations filtration rate assessment provided different results for all clearance intervals used in drug dosing. This may mean, as appropriate, over- and under-dosing of medication, with different consequences on patients. For some drugs, preventing dosing errors can be achieved by monitoring their serum concentration. For drugs with raised nephrotoxicity and for individual patients in whom kidney function estimates vary, the best option for the physician is to determine glomerular filtration rate or creatinine clearance.

Finding a rapid method for assessing renal function that can be used for all categories of patients is however necessary.

The main limitation of our study was that we did not have gold standard measurements for GFR values in order to investigate whether the employed estimating methods could be interchangeably used.

Other study limitations were the relatively small sample size, the very wide case mix of diseases, the fact that the population enrolled was not selected randomly, but based on the availability of the required variables to estimate GFR using the Cockcroft-Gault and MDRD equations.

Conclusions

The present study confirms the existence of significant differences between aCG and aMDRD equations, a result which supports the conclusion that they can not be used interchangeably in clinical practice.

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References

1. Alagiakrishnan, K., Senthilselvan, Low agreement between the Modified Diet and Renal Disease formula and the Cockcroft-Gault formula for assessing chronic kidney disease in cognitively impaired elderly outpatients. *Postgrad Med*, 2010, 122, 41-45.
2. Beddhu S, Samore MH, Roberts MS, Creatinine production, nutrition, and glomerular filtration rate estimation. *J Am Soc Nephrol*, 2003, 14, 1000-1005.
3. Bland JM, Altman DG, Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1986, 1, 307-310.
4. Botev R, Mallie JP, Couchoud C, Estimating glomerular filtration rate: Cockcroft-Gault and Modification of Diet in Renal Disease formulas compared to renal inulin clearance. *Clin J Am Soc Nephrol*, 2009, 4, 899-906.
5. Buitrago F, Calvo JJ, Gomez-Jimenez C, Comparison and agreement of the Cockcroft-Gault and MDRD equations to estimate glomerular filtration rate in diagnosis of occult chronic kidney disease. *Nefrologia*, 2008, 28, 301-310.

6. Cirillo M, Anastasio P, De Santo NG, Relationship of gender, age, and body mass index to errors in predicted kidney function. *Nephrol Dial Transplant*, 2005, 20, 1791-1798.
7. Cockcroft DW, Gault MH, Prediction of creatinine clearance from serum creatinine. *Nephron*, 1976, 16, 31-41.
8. Coresh J, Selvin E, Stevens LA, Prevalence of chronic kidney disease in the United States. *JAMA*, 2007, 298, 2038-2047.
9. Du Bois E, Du Bois D, A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med*, 1916, 17, 863-871.
10. Froissart M, Rossert J, Jacquot C, Predictive performance of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol*, 2005, 16, 763-773.
11. Geddes CC, Woo YM, Brady S, Glomerular filtration rate - what is the rationale and justification of normalizing GFR for body surface area? *Nephrol Dial Transplant*, 2008, 23, 4-6.
12. Gill J, Malyuk R, Djurdjev O, Use of GFR equations to adjust drug doses in an elderly multi-ethnic group - a cautionary tale. *Nephrol Dial Transplant*, 2007, 22, 2894-2899.
13. Hassan Y, Al-Ramahi RJ, Aziz NA, Adverse drug events in hospitalized patients with chronic kidney disease. *Int J Clin Pharmacol and Therap*, 2010, 48, 571-576.
14. Helou R, Should we continue to use the Cockcroft-Gault formula? *Nephron Clin Pract*, 2010, 116, c172-c186.
15. Levey AS, Bosch JP, Lewis JB, A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*, 1999, 130, 461-470.
16. Levey AS, Greene T, Kusek JW, A simplified equation to predict GFR from serum creatinine. *J Am Soc Nephrol*, 2000, 11, 155A.
17. Michels WM, Groonterdorst DC, Verduijn M, Performance of the Cockcroft-Gault, MDRD, and New CKD-EPI Formulas in Relation to GFR, age, and body Size. *Clin J Am Soc Nephrol*, 2009, 6, 951-953.
18. Myles PS, Using the Bland-Altman method to measure agreement with repeated measures. *BJA*, 2007, 99, 309-311.
19. National Kidney Foundation, K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis*, 2002, 39 (Suppl 1):S1-S266.
20. Péquignot R, Belmin J, Chauvelier S, Renal function in older hospital patients is more accurately estimated using the Cockcroft-Gault formula than the Modification Diet in Renal Disease formula. *J Am Geriatr Soc*, 2009, 57, 1638-1643.
21. Rimon E, Kagansky N, Cojocaru L, Can creatinine clearance be accurately predicted by formulae in octogenarian in-patients? *QJM*, 2004, 97, 281-287.
22. Rostoker G, Andrivet P, Pham I, A modified Cockcroft-Gault formula taking into account the body surface area gives a more accurate estimation of the glomerular filtration rate. *J Nephrol*, 2007, 20, 576-585.
23. Stevens LA, Nolin TD, Richardson MM, Comparison of drug dosing recommendations based on measured GFR and kidney function estimating equations. *Am J Kidney Dis*, 2009, 54, 33-42.
24. Stevens LA, Schmid CH, Zhang YL, Development and validation of GFR-estimating equations using diabetes, transplant and weight. *Nephrol Dial Transplant*, 2010, 25, 449-457.
25. Wargo KA, Eiland EH, Hamm W, Comparison of the Modification in Diet and Renal Disease and Cockcroft Gault equations for antimicrobial dosage adjustment. *Ann Pharmacother*, 2006, 40, 1248-1253.
26. *** KDOQI Clinical Practice Guidelines for chronic kidney disease: evaluation, classification, and stratification.

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