The Cockroft-Gault equation is better than the MDRD equation for estimating glomerular filtration rate in patients with advanced chronic renal failure

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SUMMARY

The aim of this study was to compare the accuracy of three kidney function estimating equations: classic Cockcroft-Gault (classic CG), corrected Cockcroft-Gault (corrected CG) and simplified Modification of Diet in Renal Disease (MDRD), in patients with advanced chronic renal failure. The study was made in 84 nondialyzed patients with chronic renal disease in stage 4 or 5. The glomerular filtration rate was measured on a 24-hour urine collection as the arithmetic mean of the urea and creatinine clearances (CUrCr). In each patient, the difference between each estimating equation and the measured glomerular filtration rate was calculated. The absolute difference expressed as a percentage of the measured glomerular filtration rate indicates the intermethod variability. In the total group the glomerular filtration rate measured as the CUrCr was de 13.5 ± 5.1 ml/min/1.73 m^2; and the results of the estimating equations were: classic CG 14.2 ± 5 ($p < 0.05$); corrected CG 12 ± 4.2 ($p < 0.01$) and MDRD: 12.1 ± 4.8 ml/min/1.73 m^2 ($p < 0.01$). The variability of the estimating equations was 15.2 ± 12.2%, 17.1 ± 13.4% and 19.3 ± 13.3% ($p < 0.05$), for classic CG, corrected CG and MDRD respectively. The percent of estimates falling within 30% above o below the measured glomerular filtration rate was 90% for CG classic, 87% for corrected CG and 79% for MDRD. The intraclass correlation coefficients respect to CUrCr were 0.86 for classic CG, 0.81 for corrected CG and 0.77 for MDRD. The MDRD variability, but not classic CG variability or corrected CG variability, showed a positive correlation with the glomerular filtration rate ($r = 0.25$, $p < 0.05$). In patients with chronic renal disease in stage 5, the variability of the different estimating equations was similar. We conclude that in our population with advanced chronic renal failure the classic CG equation is more accurate than the MDRD equation. Corrected CG equation has not any advantage respect to classic CG equation.

Key words: ***Glomerular filtrarion rate. Cockcroft-Gault equation. MDRD equation. Chronic renal failure.***

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LA ECUACIÓN DE COCKCROFT-GAULT ES PREFERIBLE A LA ECUACIÓN MDRD PARA MEDIR EL FILTRADO GLOMERULAR EN LA INSUFICIENCIA RENAL CRÓNICA AVANZADA

RESUMEN

El objetivo del presente trabajo es el estudio del grado de concordancia entre el filtrado glomerular medido como la media aritmética de los aclaramientos de urea y creatinina (AclUrCr), y las ecuaciones de Cockcroft-Gault clásica (CG clásica), Cockcroft-Gault corregida (CG corregida) y MDRD abreviada, en una población de enfermos con enfermedad renal crónica en estadio 4 y 5. El estudio ha sido realizado en 84 enfermos atendidos en la consulta de prediálisis. La variabilidad intermétodo ha sido estudiada mediante la diferencia relativa (100 x diferencia absoluta/media de los métodos analizados). En el grupo total, el filtrado glomerular considerado como la media de los aclaramientos de urea y creatinina fue de 13,5 ± 5,1 ml/min/1,73 m^2*; y el resultado de las diferentes ecuaciones fue: CG clásica 14,2 ± 5 (p < 0,05); CG corregida 12 ± 4,2 (p < 0,01) y MDRD 12,1 ± 4,8 ml/min/1,73 m*^{2}* (p < 0,01). La variabilidad intermétodo de las diferentes ecuaciones con respecto al AclUrCr fue de 15,2 ± 12,2%, 17,1 ± 13,4% y 19,3 ± 13,3% (p < 0,05), para CG clásica, CG corregida y MDRD respectivamente. El porcentaje de mediciones que caen dentro del 30% por encima o por debajo del valor conseguido con el método de referencia fue del 90% de las mediciones realizadas con la ecuación CG clásica, del 87% con la ecuación CG corregida y del 79% de las realizadas con la ecuación MDRD abreviada. El coeficiente de correlación intraclase entre la media de los aclaramientos de urea y creatinina y las distintas ecuaciones fue 0,86 para la ecuación CG clásica, 0,81 para la CG corregida y 0,77 para la MDRD. La variabilidad de la ecuación MDRD, pero no la de las otras dos ecuaciones, mostró un correlación positiva, con el filtrado glomerular (a mayor filtrado glomerular mayor variabilidad) (r = 0,25, p < 0,05). En los enfermos con insuficiencia renal crónica en estadio 5 (n = 59), la variabilidad intermétodo fue similar en las tres ecuaciones analizadas. Podemos concluir que en nuestra población con insuficiencia renal crónica avanzada, la ecuación CG clásica tiene mejor equivalencia con el filtrado glomerular medido como la media de los aclaramientos de urea y creatinina, que la ecuación MDRD abreviada. La ecuación CG corregida no mejora el grado de concordancia y por tanto no aporta ninguna ventaja sobre la CG clásica.*

Palabras clave: ***Filtrado glomerular. Ecuación Cockcroft-Gault. Ecuación MDRD. Insuficiencia renal crónica.***

INTRODUCTION

Classification of chronic renal disease is done by quantifying glomerular filtration.[1] The reference method to calculate glomerular filtration is by inulin clearance, although clearance of other exogenous compounds, usually radio-labeled, may be used as an alternative method.[2] These procedures cannot be applied in routine clinical practice. In patients with advanced renal failure a correlation has been shown between glomerular filtration and the arithmetic mean of urea and creatinine clearance.[3-6] Canadian, European, and Australian guidelines recommend this method to measure glomerular filtration rate in this type of patients.[7-10]

In order to avoid collecting the urine for 24 hours, several formulas have been created to estimate glomerular filtration rate from plasma level of creatinine and other analytical, demographical, and anthropometrical variables. The most frequently used ones are Cockcroft-Gault formula (CG)[11] standardized for 1.73m^2 and the abbreviated formula derived from the MDRD (Modification of Diet in Renal Disease) study.[12] The CG equation is obtained with four parameters (creatinine serum level, age, weight, and gender), and the abbreviated MDRD equation with four other parameters (creatinine serum level, age, gender, and black race).

Comparison of both CG and MDRD equations is controversial. A recent review on this topic[13] concluded that most of the results favor the MDRD equation, although there are contradictory studies.[14-18] The method used to determine creatinine level[19.20] and characteristics of the population analyzed may explain these discrepancies.

CG equation really is an estimation of creatinine clearance. Some authors introduce a correction factor in the classical CG equation to compensate for the effect of tubular secretion of creatinine and make it closer to glomerular filtration.[6,14,15,21]

The present work shows the study on the degree of agreement or equivalence between glomerular filtration measured as the mean of urea and creatinine clearance and the following equations: classical Cockcroft-Gault 's, corrected Cockcroft-Gault' s, and abbreviated MDRD, in a population of patients with renal disease at stages 4 and 5.

Table I. Age and anthropometrical parameters of the patients, and result for glomerular filtration with the different methods

	Mean ± SD	Range
Age (years)	63.4 ± 14.2	30-85
Weight (kg)	71.8 ± 11.7	50-104.5
Height (cm)	163.3 ± 8.8	145-188
BMI (kg/m^2)	26.9 ± 4	19.8-38.8
BSA (m^2)	1.77 ± 0.17	1.46-2.31
UrCrCl (mL/min/1.73 m^2)	13.5 ± 5.1	(4.2-26.8)
Classical CG (ml/min/1.73 m^2)	14.2 ± 5	(5.5-26.3)
Corrected CG (ml/min/1.73 m^2)	12 ± 4.2	(4.6-22.1)
MDRD (ml/min/1.73 m^2)	12.1 ± 4.8	(4.2-29.2)

BMI: Body mass index.
BSA: Body surface area.
UrCrCl: Arithmetic mean of urea and creatinine clearances from urine. Classical CG: Creatinine clearance by the Cockcroft-Gault equation. Corrected CG: classical CG equation multiplied by 0.84.
MDRD: Glomerular filtration by the abbreviated equation from the MDRD study (4 variables).

MATERIAL AND METHODS

This a retrospective study done on patients with chronic renal disease stages 4 and 5 attending the Pre-dialysis Clinic between January of 2005 and March of 2006.

Urea and creatinine clearance was calculated by collecting 24-hour urine before blood sampling. Patients previously received verbal and written instructions for correct urine collection. At the time of doing blood sampling, they were systematically asked about adequate urine collection; in case of suspecting collection errors, the sample was rejected for study. The Cockcroft-Gault formula includes weight, so that patients with suspicion of volume overload (presence of edema or ascites) were also excluded. *None of studied patients had severe liver disease, morbid obesity [body mass index (BMI) ≥ 40 m/kg^2), hyponutrition (BMI ≤ 18.5 m/kg^2) or limb amputations.* Body surface area was calculated for each patients according to the Dubois and Dubois equation.[22] One single measurement has been studied for each patient (the first valid sample during the period analyzed).

Glomerular filtration rate was calculated as the arithmetic mean of urea and creatinine clearance, and was corrected for a body surface area of 1.73m^2 (UrCrCl). At the same time, an estimation was done by using the classical CG equation,[11] CG equation multiplied by a correction factor of 0.84 (Corrected CG),[6] and the abbreviated MDRD equation.[12] Classical CG and corrected CG were standardized for a body surface area of 1.73m^2; the MDRD equation already provides an estimate of glomerular filtration corrected for a standard surface area of 1.73m^2.

Serum and urine creatinine levels were determined by the modified Jaffé's kinetic reaction, and together with urea levels they were automatically done by a Synchron CX® system from Beckman Coulter Inc, Fullerton, California. The internal variation coefficients were as follows: serum creatinine: 2.4%; urine creatinine 2.3%; serum urea 6.7%; urine urea 3.1%.

Statistical analysis: the results are expressed as mean ± standard deviation (SD). *The data analyzed have a normal distribution (Kolmogorov-Smirnov test), so that parametric tests were used.* The normal and absolute differences between the value of each one of studied methods (Classical CG, Corrected CG, and MDRD) and UrCrCl were calculated for each patient. The normal difference shows the tendency of each method to under or overestimate the UrCrCl value (bias). The absolute difference is an index of the magnitude of the error (dispersion). The absolute difference expressed as percentage of the arithmetic mean between the UrCrCl and the method analyzed indicates the inter-method variability (accuracy) and reduces the effect of the glomerular filtration value on the difference. The 50th, 75th, and 90th percentiles for the absolute difference and the variability are established. Also expressed is the percentage of measurements that lie within the 10th (P10), 30th (P30), and 50th (P50) percentiles, above or below the value yielded by the reference method; this parameter combi-

Table II. Agreement analysis between glomerular measured as the arithmetic mean of urea and creatinine clearance from urine (UrCrCl) and the classical Cockcroft-Gault (Classical CG), corrected Cockcroft-Gault (Corrected CG), and the abbreviated MDRD equations

	Classical CG	Corrected CG	MDRD
Normal difference (mL/min/1.73[2])			
Mean ± SD	0.7 ± 2.6	-1.6 ± 2.5*	-1.5 ± 3.1*
Confidence interval	(0.1; 1.3)	(-2.1; -1)	(-2.1; -0.8)
Absolute difference (mL/min/1.73[2])			
Mean ± SD	2 ± 2.7	2.2 ± 2	2.5 ± 2.3
Percentile 50	1.4	1.5	1.8
Percentile 75	2.8	2.9	3.8
Percentile 90	4.6	4.8	5.1
Variability (%)			
Mean ± SD	15.2 ± 12.2	17.1 ± 13.4	19.3 ± 13.3**
Percentile 50	10.4	12.1	17.3
Percentile 75	22	23.3	26.1
Percentile 90	28.4	37.5	38.5

*p < 0.001 as compared to classical CG.
**p < 0.05 as compared to classical CG.

nes bias and accuracy, and has been established by the KDOQI guidelines as the best criterion to compare the different equations estimating the glomerular filtration rate.[23] The correlation between the different methods was done by the Pearson's correlation coefficient. The agreement analysis was completed by the Bland-Altman's construct and the inter-class correlation coefficient, which is another test to study the degree of equivalence between different measuring methods.[24]

The student's t test for paired and non-paired data has been used for means comparison. Percentage comparison has been done by the Chi-squared test. P values < 0.05 have been considered as being statistically significant.

RESULTS

This study was done on 84 patients (55 males and 29 females). Seven patients came from South America (Ecuador and Peru) one from Romania, and the remaining were born in Spain. None of them was of black ethnicity or had limb amputations. The etiology of renal failure was diabetes 21%, polycystic renal disease 16%, vascular 14%, interstitial 11%, glomerulonephritis 8%, unknown 12%, and other conditions 18%.

Age, anthropometrical data, and values of glomerular filtration from the different methods used in each patient are shown in Table I. The four methods yield different results: $p < 0.05$ between UrCrCl and classical CG; $p < 0.001$ between UrCrCl and corrected CG, between UrCrCl and MDRD, between classical CG and corrected CG, and between classical CG and MDRD. There are no statistically significant differences between corrected CG and MDRD.

There is a good correlation between UrCrCl and the different estimation equations: $r = 0.87$ by the classical CG ($p < 0.001$), $r = 0.87$ by the corrected CG ($p < 0.001$), and $r = 0.81$ by MDRD ($p < 0.001$).

Table II shows agreement studies between glomerular filtration measured as the mean urea and creatinine clearance and the different estimation equations. The classical CG estimation equation has positive bias and mildly overestimates the value of UrCrCl, with a mean difference of 0.7 mL/min/1.73m^2. For corrected CG and MDRD equations, there is a negative and the mean difference is, respectively, -1.6 and -1.5 mL/min/1.73m^2. The lowest variability corresponds to the classical CG equation. The distribution by percentiles of the absolute difference and the variability is also better for the classical CG equation.

Table III expresses the percentage of measurements lying within P10, P30, and P50 of the value yielded by the reference method. Again the data are better with the classical CG equation: 48% of the patients have a value by the classical CG equation that lies within the 10th percentile above or below the value from the reference method, and 90% lie within the 30th percentile above or below that value.

The variability of the classical CG, corrected CG or MDRD equations was not influenced by gender or age (data not shown). The variability of the classical CG and corrected CG equations did not correlate with glomerular filtration (measured as UrCrCl) ($r = -0.14$ and $r = 0.18$, respectively, p = N.S.). By contrast, the variability of the MDRD equation showed a positive correlation, weak but significant,

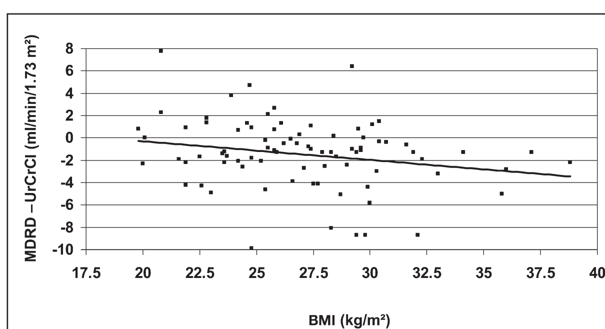

Fig. 1.—Correlation between the normal difference between the abbreviate d MDRD equation. And the arithmetic mean of urea and creatinine clearance from ur ine (UrCrCl), and body mass index (BMI) (r = -0.23; p < 0.05).

Table III. Percentage of measurements lying within the 10^{th} (P10), 30^{th} (P30), and 50^{th} (P50) percentiles, above or below the value yielded by the gold standard method

	Classical CG	Corrected CG	MDRD
P10	48	37	29**
P30	90	87	79*
P50	99	96	99

*p < 0.05 as compared to classical CG.
**p < 0.01 as compared classical CG.

with glomerular filtration (the greater the glomerular filtration the greater the variability) ($r = 0.25$, $p < 0.05$).

The level of agreement between the MDRD equation and UrCrCl is influenced by BMI. The normal difference between the MDRD equation and UrCrCl is correlated with BMI ($r = -0.23$; $p < 0.05$) (Figure 1). Median BMI was 26.6 kg/m^2; the normal difference between the MDRD equation and UrCrCl was -0.7 ± 3.1 in the group of patients with BMI below the median (n = 41) and -2.1 ± 3 in the group of patients with BMI equal or above the median (n = 43) ($p < 0.05$). That is to say, as BMI increases the MDRD equation underestimates the UrCrCl value. Both classical and corrected CG equations do not significantly correlate with BMI (data not shown).

The last agreement analysis done was the interclass correlation coefficient between the UrCrCl and the different equations. Again, the result favored the classical CG equation: interclass correlation coefficient 0.86 for classical CG, 0.81 for corrected CG, and 0.77 for MDRD equation. Figures 2 and 3 show the Bland-Altman construct for both the classical CG and MDRD equations.

Twenty-five patients had stage 4 chronic renal failure (UrCrCl 15-29 mL/min/1.73m^2) and 59 patients had stage 5 chronic renal failure (UrCrCl < 15 mL/min/1.73m^2). Table IV expresses the agreement studies by degree of chronic renal failure. In patients with stage 5 chronic renal failure, the level of agreement for all three equations was similar. Differences between them, favoring the classical CG equation, are seen in patients with stage 4 chronic renal failure.

Table IV. Agreement analyses between glomerular filtration measured as the arithmetic mean of urea and creatinine (UrCrCl) clearance from urine and the classical Cockcroft-Gault (Classical CG), corrected Cockcroft-Gault (Corrected CG), and abbreviated MDRD equations, by the stage of chronic renal failure. Data are expressed as mean ± SD

Stage 4 Chronic renal failure (n = 25)			
	Classical CG	Corrected CG	MDRD
Normal difference (mL/min/1.73^2)	-0.2 ± 3.1	-3.3 ± 2.8*	-2.9 ± 4.6*
Absolute difference (mL/min/1.73^2)	2.5 ± 1.8	3.5 ± 2.6***	4.6 ± 2.9*
Variability (%)	12.8 ± 9.3	19.6 ± 14.6**	25.6 ± 16.4*
Stage 5 Chonic renal failure (n = 59)			
	Classical CG	Corrected CG	MDRD
Normal difference (mL/min/1.73^2)	1.1 ± 2.2	-0.8 ± 2*	-0.8 ± 1.8*
Absolute difference (mL/min/1.73^2)	1.9 ± 1.6	1.7 ± 1.3	1.7 ± 1.1
Variability (%)	16.2 ± 13.2	16.1 ± 12.8	16.6 ± 10.9

*p < 0.001 as compared to classical CG.
**p < 0.01 as compared to classical CG.
***p < 0.05 as compared to classical CG.

DISCUSSION

In the present study done on patients with chronic renal failure at stages 4 and 5 we analyzed the level of agreement between the classical CG, corrected CG and MDRD equations as compared to the gold standard method used to measure glomerular filtration rate in these patients, which was the arithmetic mean of urea and creatinine clearances. *We only analyzed those cases in which there was the certainty that urine had been correctly collected by means of a driven questionnaire.*

Pearson's correlation coefficient, normal difference, absolute difference, variability, and several percentiles of the last two parameters, the percentage of patients whose variability was below P10, P30, AND P50, as well as the interclass correlation coefficient indicate that the classical CG equation has a better level of agreement with the gold standard method, as compared with the MDRD equation. The corrected CG equation ranks in a intermediate position between the classical CG and the MDRD equations. KDOQI guidelines recommend using the P30 to compare different equations estimating glomerular filtration rate.[23] Whereas in the MDRD study 91% of the measurements laid within the P30, below or above the reference method,[25] in our study the P30 comprised 90% of the measurements performed with the classical GC equation, 87% with the corrected CG equation, and 79% of those done with the abbreviated MDRD equation. With a parameter such as glomerular filtration rate, measurements lying within

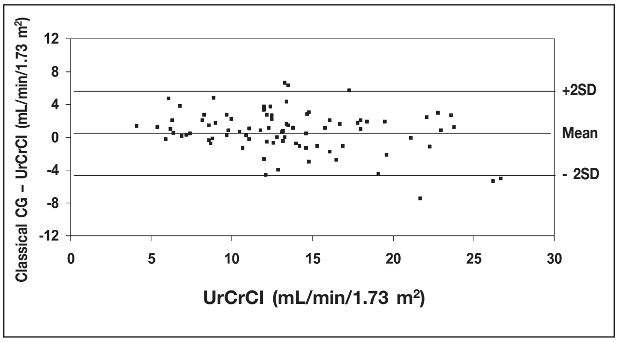

Fig. 2.—Bland-Altman's construct between the classical Cockcroft-Gault equation (classical CG) and the arithmetic mean of urea and creatinine clearances (UrCrCl).

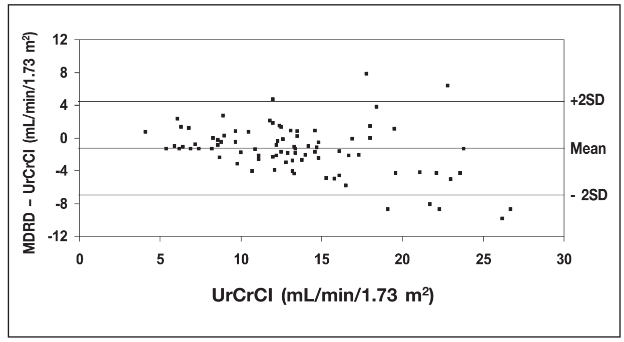

Fig. 3.—Bland-Altman's construct between abbreviated MDRD equation and the arithmetic mean of urea and creatinine clearances (UrCrCl).

the P10, above or below the gold standard method, indicate total equivalence. The P10 was 48% for the classical CG equation and 29% for the abbreviated MDRD equation.

The MDRD study was done on a North American population with different anthropometrical characteristics from Spanish populations. Mean weight for the population of the MDRD study[6] was 79.6 ± 16.8 kg and body surface area 1.91 ± 0.23 m^2. In our population, mean weight was 71.8 ± 11.7 kg and body surface area 1.77 ± 0.17 m^2. Both parameters are statistically different from those in the MDRD population ($p < 0.001$ for both). The MDRD formula does not contain any anthropometrical parameter and, thus, it is not surprising that its accuracy level is different in a population with different anthropometrical differences. Most of the studies in which the MDRD equation has not been shown to be of better value than the CG equation were done in populations different from the North American one.[14,15,17,18]

Barroso *et al.* have recently published a study similar to ours, in which they used blood clearance of Tc99mDTPA as the gold standard method to measure glomerular filtration, and they also used the original MDRD equation with seven variables.[18] Age and anthropometrical characteristics of their population are very similar to ours, and their results are similar to ours. In the Spanish population with advanced chronic renal failure, the classical CG equation presents better accuracy than the MDRD equation to measure glomerular filtration, either if the arithmetic mean of urea and creatinine clearances in urine or blood clearance of Tc99mDTPA are used as the gold standard method.

In most of the comparative analysis performed, it is shown that the classical CG equation overestimated glomerular filtration.[18,21,26-28] The classical CG equation really predicts creatinine clearance, which exceeds glomerular filtration as a result of creatinine tubular secretion. In order to compensate for this effect, it has been recommended to introduce a correction factor in the classical CG equation.[6,14,15,21] The corrected CG equation improves the level of agreement with glomerular filtration in some studies.[14,15,21] In our work, corrected CG does not provide any advantage at all; its level of agreement is slightly better than that for the MDRD equation and lower than that achieved with the classical CG equation.

Beddhu *et al.*[29] have verified that nutritional status introduces an important bias in MDRD equation. The MDRD value negatively correlates with nutritional status: well-nourished patients have disproportionately lower MDRD vales than patients with poor nutritional status. These data have been corroborated by our study: as BMI increases the MDRD equation further underestimates the glomerular filtration value measured as the arithmetic mean of urea and creatinine clearance. That is to say, in patients having the same glomerular filtration, the MDRD value will be different depending on the BMI. By contrast, the accuracy of the CG equation is not influenced by the BMI.

Taking in mind the limitations due to the number of cases analyzed, we may conclude that in our population with advanced chronic renal failure, the classical CG equation has better equivalence with glomerular filtration measured as the mean of urea and creatinine clearance than the abbreviated MDRD equation. We may point out that for stage 5 chronic renal failure, the level of agreement between both formulas is similar, and thus the indication for starting on renal replacement therapy may be established with any of both formulas. Contrary to what has been observed by others, the corrected CG equation does not improves the level of agreement, and thus does not provides any benefit over the classical CG equation.

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