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Accuracy of indirect determinations of glomerular filtration in advanced renal failure

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SUMMARY

Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) formula are indirect estimates of renal function which have been widely accepted, though their accuracies have been scarcely validated in advanced chronic renal failure. The purpose of this study was to determine the accuracy (bias and precision) of these formulas in advanced CRF patients.

The study group consisted of 99 unselected patients (62 ± 15 years, 59 females) with advanced CRF. The glomerular filtration rate (GFR) was measured by Tc^{99m} DTPA. Simultaneously, estimates of GFR by CG corrected for 1.73 m^2 and MDRD (formula 7) were calculated. Agreement was evaluated graphycally, bias was assessed by mean and median difference, and precision by median absolute differences and Bland-Altman plots.

Mean GFR by DTPA, CG and MDRD were: 16.24 ± 4.38 and 16.77 ± 4.65 and 13.58 ± 4.27 ml/min/1.73 m^2, respectively. MDRD equation significantly underestimated GFR-DTPA (p = 0.0001). Both CG and MDRD correlated significantly with GFR-DTPA (R = 0.53 and R = 0.62, respectively). CG formula performed better than the MDRD equation with respect to bias (0.30 vs *–3.24 ml/min/1.73 m^2, p = 0.0001), and precision (0.58* vs *–3.11 ml/min/1.73 m^2, p = 0.0001). By multiple linear regression, the best determinants of the error of the estimation by CG formula were: serum creatinine (beta = -0.58; p < 0.0001), age (beta = -0.62; p < 0.0001), and body mass index (beta = 0.26, p = 0.004), and by MDRD formula were: serum creatinine (beta = -0.38; p < 0.0001), and body mass index (beta = -0.20, p = 0.03).*

In conclusion, in unselected patients with advanced chronic renal failure, estimates by CG formula were more accurate than those obtained by MDRD formula. Serum creatinine was the main source of error of the estimation of GFR by both formulas, though demographic and anthropometric characteristics influenced as well on their accuracies.

Key words: ***Cockcroft-Gault formula. Chronic renal failure. Glomerular Filtration Rate. MDRD equation.***

EXACTITUD DE LAS ESTIMACIONES INDIRECTAS DEL FILTRADO GLOMERULAR EN LA INSUFICIENCIA RENAL AVANZADA

RESUMEN

Las ecuaciones de Cockcroft-Gault (CG) y MDRD son estimaciones indirectas de la función renal de amplia aceptación, pero que han sido escasamente vali-

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dadas en los estadios más avanzados de la insuficiencia renal crónica (IRC). El objetivo del presente estudio fue establecer la exactitud (sesgo y precisión) de estas estimaciones en pacientes con IR avanzada.

Se estudiaron 99 pacientes (59 mujeres, edad media 62 ± 15 años), con IRC avanzada prediálisis. Se recogieron datos demográficos, comorbilidad, peso, talla, creatinina, urea, y albúmina. El filtrado glomerular (FG) se midió con Tc^{99m} DTPA (FG-DTPA). Simultáneamente se estimó el FG con las fórmulas de CG corregido a 1,73 m^2 y MDRD (fórmula 7). Se determinó la exactitud de cada una de las fórmulas analizando el grado de correlación, sesgo (diferencia de media y mediana), y precisión (mediana de las diferencias absolutas y método de Bland-Altman).

El FG-DTPA, y los estimados por CG y MDRD fueron respectivamente: 16,24 ± 4,38; 16,77 ± 4,65 y 13,58 ± 4,27 ml/min/1,73 m^2. FG-MDRD infraestimó significativamente el FG-DTPA (p < 0,0001). La diferencia de la mediana fue más amplia con FG-MDRD (-3,24 frente 0,30 ml/min/1,73 m^2, p = 0,0001), al igual que la mediana de las diferencias absolutas (-3,11 frente 0,58 ml/min, p = 0,0001). Los mejores determinantes del error FG-CG fueron: la creatinina (beta = -0,58; p < 0,0001), la edad (beta = -0,62; p < 0,0001), y el índice masa corporal (beta = -0,26; p = 0,004). Los mejores determinantes del error FG-MDRD fueron: creatinina (beta = -0,38; p < 0,0001), y el índice masa corporal (beta = -0,20; p = 0,035).

En conclusión, en pacientes no seleccionados con IRC avanzada la estimación del FG con CG corregida a 1,73 m^2 fue menos sesgada y más precisa que con MDRD. La creatinina sérica fue la principal fuente de error en la estimación del FG con ambas fórmulas, aunque las características demográficas y antropométricas también influyeron.

Palabras clave: ***Algoritmo Cockcroft-Gault. Algoritmo MDRD. Filtrado glomerular. Insuficiencia Renal Crónica.***

INTRODUCTION

Glomerular filtration is the best parameter to establish the level of severity of renal failure and one of the most qualified criteria for deciding when to start on a renal replacement therapy program.[1] The methods for directly measuring GF (inulin clearance, radio-markers, etc.) are very cumbersome for routinary use. Creatinine clearance measurement may have errors, mostly due to collection of urine sample. With the aim of making this task easier and avoiding urine collection, widely accepted algorithms such as Cockcroft-Gault's[2] (CG) or «Modification Diet Renal Disease» (MDRD)[3] have been developed.

With both formulas GF estimation largely lies on serum creatinine (Cr). Thus, estimation uncertainties will depend on factors different from GF that may vary Cr.

The calibration of the technique used to measure Cr is an important determinant of the estimation error of GF, especially when Cr ranges within normal limits.[4]

When these formulas are used in patients with renal failure, it should be taken into account that populations used in the original studies that developed them were highly selected. The MDRD study excluded patients older than 70 years, diabetics on insulin therapy, patients with Cr higher than 7 mg/dL, and those having a «chronic condition».[5] On the other hand, in the original study by Cockcroft and Gault 90% of the 236 included patients were male in whom creatinine clearance was measured with no correction for standard body surface area.[2]

Some study has shown that the accuracy in GF estimation by the MDRD formula is slightly higher for patients with severe renal failure or diabetics.[6]

The aim of this study was to analyze the exactness (bias and accuracy) of both formulas in 99 patients with advanced renal failure, and to establish determinants for deviations in GF estimation in relation to a highly reliable standard.

MATERIAL AND METHODS

Patients

Ninety-nine prevalent patients with advanced renal failure at the predialysis clinic were studied du-

ring the period comprised between November of 2003 and April of 2004. Mean age was 62 ± 15 years (59 women and 40 men). There were no exclusion criteria. The cause for renal failure was: unknown (30 patients), glomerulopathy (17 patients), diabetic nephropathy (20 patients), chronic interstitial nephropathy (22 patients), polycystic disease (4 patients), ischemic nephropathy (3 patients), and other diagnoses (1 patient).

All patients were on a stable clinical situation, with the following estimated comorbidity indexes assessed by the Davies' method: grade 0 (51%), grade 1(44%) and grade 2 (5%).

There were no ethnic differences in the study group, all of them being Caucasians. Anthropometrical characteristics were: mean weight 72 ± 14 kg; height 1.61 ± 0.10 m, body mass index 27.8 ± 5.4 kg/m^2, and body surface area 1.75 ± 0.19 m^2.

Measurement and estimation of glomerular filtration

All patients had a glomerular filtration (GF) determination by isotopic dilution with Diethylene Triamine Penta Acetic Acid labeled with Tc^{99m} (Tc^{99m}DTPA). An intravenous dose of 50 µCi/kg was administered and blood samples were drawn at 120, 180, and 240 minutes. For GF calculation, the Bröchner-Mortensen method was used.[8]

Patients were fasting and with the first blood sample urea, creatinine, and albumin were also determined (Hitachi Modular P-800 Roche Diagnostics, Germany). Creatinine was measured by the modified Jaffé's kinetic reaction, with daily calibration using multi-parameter reactives from Roche. With these parameters, creatinine clearance was estimated by Cockcroft-Gault's formula, correcting the result for a body surface area of 1.73 m^2.2 GF was also estimated by the MDRD formula (formula 7).[3]

Design and Statistical Methods

The study sample size was estimated for a type I error of 0.05, and type II error of 0.90, with a projected sample standard deviation of 5 mL/min, and a difference between both methods of at least 1.5 mL/min.

GF measured by DTPA was considered the best reliable standard. In order to establish the exactness of GF estimations (CG and MDRD) in relation to GF-DTPA, the following statistic parameters were analyzed: the correlation between GF estimation and measurement, which was graphically analyzed, determined by Pearson's coefficient. Bias, which was determined by the differences of the means and medians in relation to GF-DTPA. The accuracy, which was graphically analyzed by Bland-Altman method,9 and determining the medians of the absolute and percentage differences in relation to GF-DTPA and comparing the percentage of estimations that were within the 30-50% range of the GF-DTPA. For comparison of the differences of continuous variables the Student's t test was used for paired samples and the non-parametric Wilconxon's test were used. For discrete sample comparison, the McNemar test was used.

In order to determine the best determinants of deviation of GF estimation, multiple linear regression models were obtained for each one of the estimating formulas, including the following independent variables: age, gender, body mass index, diabetes, comorbidity index, urea, creatinine, and albumin.

Data are expressed as mean ± SD or median. A p value < 0.05 was considered statistically significant. The SPSS software, version 13.0, was used for analyzing statistical data.

RESULTS

Results of studied laboratory parameters are shown in table I. Mean GF-CG was similar to mean GF-DTPA, but mean GF-MDRD was significantly lower.

Figures 1 and 2 show the correlations between estimated GF and GF-DTPA. The correlation coefficient was slightly better for MDRD estimation than for CG estimation.

Figures 3 and 4 and table II show the data on bias and accuracy. The bias was significantly lower with CG estimation than with MDRD estimation (differences of the medians of frequency distribution). The accuracy estimated by absolute and percentage differences from estimations by GF-DTPA was also better for CG formula than for MDRD formula. However, the estimated accuracy as percentage of values within the 30-50% range of GF-DTPA was similar with both formulas (fig. 5).

There was a significant correlation between deviations of both estimations in relation to GF-DTPA ($r = 0.80$; $p < 0.0001$), indicating that the magnitude of the error was in agreement with both estimations.

Table III shows the best determinants of the deviation for each estimation in relation to GF-DTPA. Creatinine was the main source of error when estimating GF with both formulas. More specifically, with the CG formula, Cr and age tended to underestimate, whereas body mass index tended to overestimate GF-DTPA. On the other hand, with MDRD

Table I. Results of studied laboratory parameters

Urea, mg/dl	151 ± 51
Creatinina, mg/dl	4.27 ± 1.21
Albumin, g/dl	3.96 ± 0.42
Glomerular filtration DTPA, ml/min/1,73 m^2	16.24 ± 4.38
Glomerular filtration CG, ml/min/1,73 m^2	16.76 ± 4.65
Glomerular filtration MDRD, ml/min/1,73 m^2	13.59 ± 4.27*

*p < 0.0001 MDRD *vs* DTPA

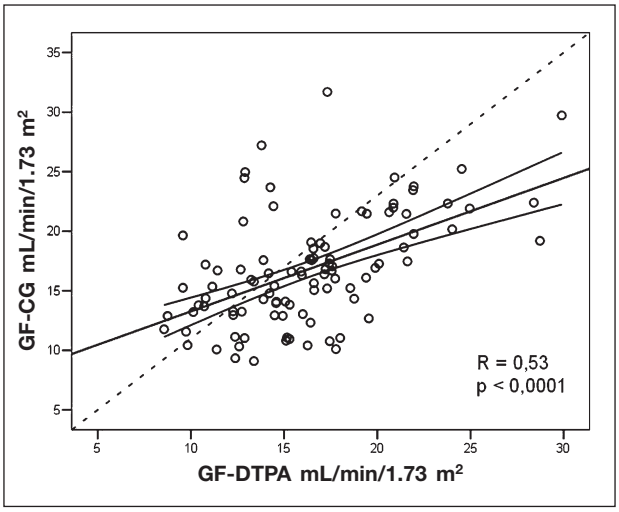

Fig. 1.—Linear correlation between estimation of glomerular filtration by Cockcroft-Gault (GF-CG) and GF measured by DTPA (GF-DTPA). The identity line (dotted) and the regression line (continuous) with 95% confidence intervals are represented in the graph.

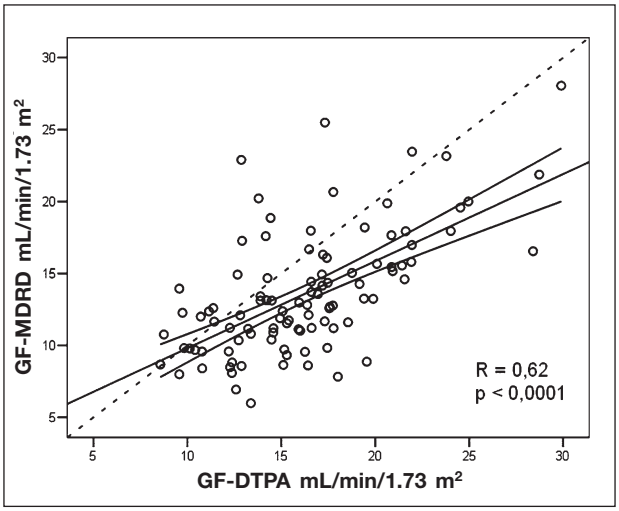

Fig. 2.—Linear correlation between estimation of glomerular filtration by MDRD (GF-MDRD) and GF measured by DTPA (GF-DTPA). The identity line (dotted) and the regression line (continuous) with 95% confidence intervals are represented in the graph.

formula, Cr and body mass index tended to underestimate GF-DTPA.

Diabetes diagnosis or comorbidity level did not have a significant influence on the magnitude of the deviations of GF estimations.

DISCUSSION

This study results show that GF estimation in this group of patients with advanced renal failure is less biased and slightly more accurate with the CG equation than with MDRD formula. The magnitudes of the inaccuracies obtained with both formulas were highly correlated, which suggested common error sources. The best error determinant or deviation between estimated and measured GF was serum creatinine, both for CG and MDRD estimations.

GF by MDRD was approximately 20% underestimated in relation to GF-DTPA in this study group. This result markedly disagrees with that recently published by Poggio et al.[6] in which both MDRD and CG estimations overestimated 21-27% GF by I125-thalamate in 546 patients with advanced renal failure. The differences in population characteristics between both studies could have explained these discrepancies an, at the same time, could help interpret the results.

In the study by Poggio et al.[6], measurement of best reliability reference GF was done by I125-thalama-

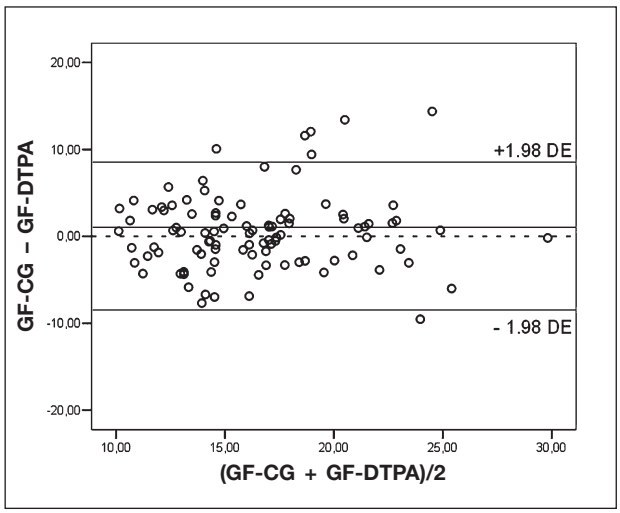

Fig. 3.—Bland-Altman graph for estimation of glomerular filtration by Cockcroft-Gault (GF-CG). The difference between CG estimation and DTPA measurement is shown in the Y axis. The half-sum of the estimation by CG and DTPA measurement is shown in the X axis. The identity line (dotted) and the difference of he mean with 1.98 times standard deviation (continuous) are shown in the graph.

Table II. Studied statistical parameters

Parameter	Cockcroft-Gault	MDRD	P**
Differences of the medians in relation to GF-DTPA, mL/min/1,73 m^2	0.38	-3.24	< 0.0001
Median of absolute differences in relation to GF-DTPA, mL/min/1,73 m^2	0.51 (-2.18; +2.57)*	-3.11 (-4.97; -0.72)*	< 0.0001
Median of absolute differences in relation to GF-DTPA, %	2,8 (-13.0; 17.8)	-19.8 (-28.3; -3.7)	< 0.0001
Accuracy 30% of GF-DTPA, %	75	70	NS
Accuracy 50% of GF-DTPA, %	90	96	NS

*Interquartile Ranges. **p of the differences betweenCG y MDRD.

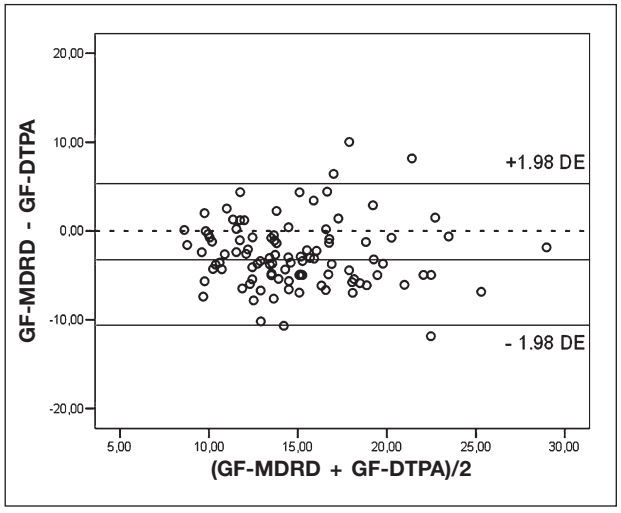

Fig. 4.—Bland-Altman graph for estimation of glomerular filtration by MDRD (GF-MDRD). The difference between MDRD estimation and DTPA measurement is shown in the Y axis. The half-sum of the estimation by MDRD and DTPA measurement is shown in the X axis. The identity line (dotted) and the difference of he mean with 1.98 times standard deviation (continuous) are shown in the graph.

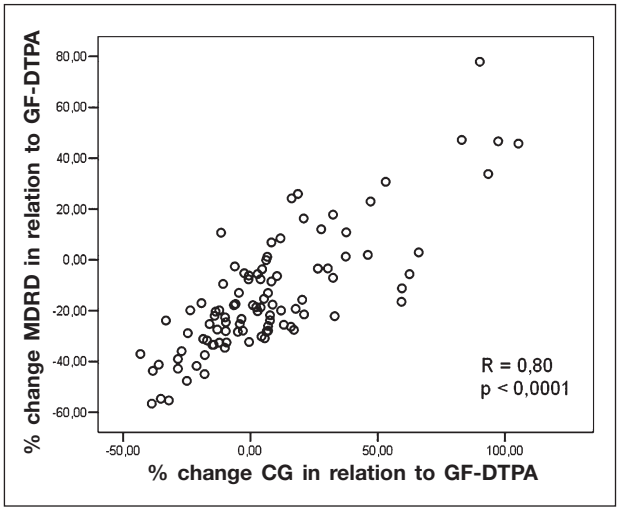

Fig. 5.—Correlation between percentage error and of the estimations (difference between estimation and GF measurement) with CG and MDRD.

te, whereas in the present study DTPA is used. Although both GF measuring methods are more accurate than endogenous substances clearance, they still have a certain degree of inaccuracy when compared with inulin clearance, especially in patients with advanced renal failure.[10] GF measurement with Cr^{51}-EDTA in continuous infusion is the recommended technique in patients with advanced renal failure,[10] although with DTPA measurement, especially when three samples are taken, and I^{125}-thalamate have a comparable accuracy.[11-13] Some studies have observed that MDRD formula underestimates GF measured by DTPA in subjects with normal renal function and in patients with moderate renal failure.[14] Since MDRD algorithm is derived from GF measurements with I^{125}-thalamate[3] it cannot be ruled out that some of the differences obtained with this formula and measurements of GF by other isotopic methods different than I125-thalamate may be due to variations of the best reliability reference. However, it seems unlikely that this circumstance would be the only reason to explain the big differences between both studies.

The differences in demographic and anthropometric characteristics may have also explained some of the discrepancies. Mean age was lower and the percentage of male patients was higher in the popula-

Table III. Multiple linear regression of the deviation of estimations with Cockcroft-Gault y MDRD formulas in relation to glomerular filtration measured by DTPA

Best determinants for Cockcroft-Gault deviations

Variable	Beta	p
Serum creatinine, *mg/dL*	-0.583	0.0001
Age, *years*	-0.624	0.0001
Body mass index, kg/m^2	+0.266	0.003

Best determinants for MDRD deviations

Variable	Beta	p
Serum creatinine, *mg/dl*	-0.377	0.0001
Body mass index, kg/m^2	-0.202	0.035

tion studied by Poggio et al.[6] as compared to the population included in our study. As shown by the regression analysis on error determinants of GF estimation in relation to GF-DTPA done in the present study (table III), age had a tendency to underestimate GF whereas overweight measured by body mass index had the opposite effect, overestimating GF-CG and underestimating GF-MDRD. The same discrepancies shown here for age and body mass index have been observed in another study.[15] These findings suggest that demographic and anthropometric characteristics of the studied population may be determinants of the accuracy of indirect GF estimations.

One of the most confusing issue in the MDRD algorithm is understanding how calculations that do not include anthropometrical data are able of estimating GF corrected for a standard body surface area.[3] This datum seems more accidental than premeditated in the original study that lead to the development of the MDRD algorithm. In this way, it seems likely that the more similar the characteristics of the studied population to the original population, the more accurate the estimation corrected for body surface area would be.

Correlation coefficients between GF estimates and measured GF were lower to those obtained in other studies (figures 2 and 3). However, these results are highly foreseeable since the linear adjustment of GF estimations with these formulas greatly depends on the range values of the sample. Thus, if we were included in our study just 4-5 estimations with GF values between 30-70 mL/min, the adjustments would be over 0.85 correlation coefficient (calculated but no shown data).

Serum creatinine was the main error source for deviations of GF estimations in relation to measured GF. This finding is not surprising since this is the parameter having the most influence on the results obtained with both formulas. Although calibration of the technique used to measure creatinine is important in GF estimations within a normal range,4 other factors such as variable creatinine tubular secretion in renal insufficiency, meat intake, or muscle mass may be key factors to explain the error in indirect GF estimations in patients with advanced renal failure.[16]

To conclude, indirect GF estimations are inaccurate in a Spanish population with advanced renal failure. The results obtained with the CG formula corrected for standard body surface area are less biased and more accurate. The main clinical application of these findings is that GF estimations are very helpful tools to determine the severity of renal failure, but due to their inaccuracy, they should be valued with flexibility when taking important decisions as for instance dialysis onset.

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