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Comparison and agreement of the Cockcroft-Gault and MDRD equations to estimate glomerular filtration rate in diagnosis of occult chronic kidney disease

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SUMMARY

Introductión and objectives: *The estimation of Glomerular Filtration Rate (GFR) by Cockroft-Gault or simplified MDRD functions is a powerful tool for the Chronic Kidney Disease (CKD) diagnosis. The aims of the present study are: 1) To analyze the accuracy between Cockroft-Gault and simplified MDRD equations in the Hidden Renal Failure (HRF) diagnosis, and 2) To know the profile and coronary risk of patients diagnosed of HRF for each equation.*

Patients and methods: *Ten year follow-up of a cross sectional study. A total of 845 patients between 35 and 74 years old (average age 55 years, 56.7% female) without evidence of cardiovascular disease and taken care in a urban primary health center. HRF was defined as an estimated GFR < 60 ml/min/1.73 m^2 in patients with normal values of creatinine (< 1.3 mg/dl in women and < 1.4 mg/dl in men).*

Results: *8.3% of studied population had HRF by Cockroft-Gault formula and 11.6% using MDRD. The HRF patients diagnosticated with Cockroft-Gault function were older (67.4* vs *64.4 years, p < 0.001) and had a higher coronary risk using either the original Framingham equation and REGICOR function. Furthermore, those HRF patients diagnosticated using MDRD function had a higher body mass index (29.6* vs *26.3 kg/m^2, p < 0.001) and were women in a greater percentage. Kappa index of agreement of these two equations for diagnosis of HRF was 0,55. The HRF patients diagnosticated exclusively by the use of Cockroft-Gault function were mainly men (75%), older (69.1 vs 61.9 years, p < 0.001) and they had a high coronary risk in the Framingham equation (32.7%) and REGICOR function (13.1%).*

Conclusions: *Cockroft-Gault and MDRD equations present a moderate agreement in HRF diagnosis (stage 3 of CKD) in patients between 35 and 74 years old. If we only use the MDRD function, a group of HRF patients would be excluded. This population was mainly male (75%), older (69 years old), with a high coronary risk estimated by original Framingham and REGICOR equations, and confirmed in the ten years follow-up of these patients.*

Key words: *Chronic kidney disease. Renal failure. Glomerular filtration. Risk factors.*

RESUMEN

***Introducción y objetivos:* La estimación del filtrado glomerular (FG) mediante fórmulas como la de Cockcroft-Gault o la derivada del estudio Modification of Diet in Renal Disease (MDRD) es una de las estrategias recomendadas en el diagnóstico de la enfermedad renal crónica (ERC). Los objetivos del presente trabajo son: 1) Analizar el grado de concordancia de las ecuaciones de Cockcroft-Gault y MDRD en el diagnóstico de ERC oculta en una cohorte seguida durante 10 años de pacientes de 35-74 años, adscritos a un centro de salud urbano, sin antecedentes de enfermedad cardiovascular y cifras normales de creatinina plasmática, y 2) Conocer el perfil y riesgo coronario de los pacientes diagnosticados de ERC oculta en cada ecuación.**

***Pacientes y métodos:* Un total de 845 pacientes (edad media 55,5 años, 56,7% mujeres). Se consideró ERC oculta la presencia de un FG < 60 ml/min/1,73 m^2 en pacientes con creatinina < 1,3 mg/dl en mujeres y < 1,4 mg/dl en varones.**

***Resultados:* Un 8,3% de la población tenía ERC oculta usando la fórmula de Cockcroft-Gault y un 11,6% según MDRD. Los pacientes con ERC oculta en la función de Cockcroft-Gault tenían más edad (67,4 años frente a 64,4, p < 0,001) y un mayor riesgo coronario, tanto en la función de Framingham original como en REGICOR, mientras que los pacientes diagnosticados de ERC por MDRD presentaban mayor índice de masa corporal (29,6 frente a 26,3 kg/m^2, p < 0,001) y una mayor proporción de mujeres (86,7% frente a 66,1%, p < 0,01). El índice kappa de concordancia entre las dos funciones en el diagnóstico de ERC oculta fue de 0,55. Los pacientes diagnosticados de ERC oculta exclusivamente con la ecuación de Cockcroft-Gault eran fundamentalmente varones (75,0%), con más edad (69,1 frente a 61,9 años, p < 0,001) y un riesgo coronario alto tanto en las funciones de Framingham original (32,7%) como en REGICOR (13,1%).**

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Conclusiones: **Las fórmulas de Cockcroft-Gault y MDRD presentan una concordancia moderada en el diagnóstico de ERC oculta (ERC estadio 3) en pacientes de 35-74 años de edad. La elección de la fórmula MDRD excluiría del diagnóstico de ERC a un grupo de población constituido mayoritariamente por varones (75%), de edades avanzadas (69 años) y un alto riesgo cardiovascular, tanto estimado en las ecuaciones de Framingham original y en REGICOR como confirmado en el seguimiento de diez años.**

Palabras clave: Enfermedad renal crónica. Insuficiencia renal. Filtrado glomerular. Factores de riesgo. Mortalidad Cardiovascular.

INTRODUCTION

Early detection of patients with occult chronic kidney disease (CKD) is one of the measures proposed by the Spanish Society of Nephrology (SEN) and other institutions to fight against the announced epidemic of renal failure.[1,2,3] Primary care physicians and teams have a significant responsibility in early identification of patients with CKD and in optimization of their treatment in the early stages, in order to decrease the risk of progression of this disease and its associated cardiovascular morbidity. While measurement of plasma creatinine levels is the most universal routine method to assess kidney function, it is a well known fact that its relationship to glomerular filtration rate (GFR) is poor, with great creatinine clearance losses (higher than 50%) being required to detect minimum increases in plasma levels.[4] In fact, creatinine increases above the values considered normal are usually seen when marked decreases in kidney function have already occurred, particularly in elderly women and subjects with a reduced muscle mass.[5] This limitation may be overcome by measuring creatinine clearance in 24-hour urine. This method, however, not only overestimates the true GFR, but also requires an adequate urine collection, which represents a serious disadvantage for routine use in primary care practices. The K-DOQI (Kidney Disease Outcomes Quality Initiative) clinical practice guidelines[6] and the SEN[7] therefore recommend use of predictive equations to estimate GFR. Among these, particular mention should be made of the Cockcroft-Gault[8] and MDRD (derived from the Modification of Diet in Renal Disease study) equations.[9] Most comparisons favour the MDRD equation,[10] but controversy still exists, and studies have reported conflicting results.[12-15]

Based on the foregoing, a study was designed to achieve two objectives. 1) to analyse the agreement between Cockcroft-Gault and MDRD equations in diagnosis of occult CKD in a cohort of patients aged 35-74 years attending an urban health centre with no history of cardiovascular disease and normal plasma creatinine values followed up for 10 years, and 2) to ascertain the coronary risk profile of patients diagnosed of occult CKD by each of these two equations to estimate GFR.

PATIENTS AND METHODS

An observational, follow-up study was conducted on a retrospective cohort of 845 patients (4.4% of the population assigned to the health centre) aged 35-74 years with no known history of ischemic heart disease or other cardiovascular diseases followed up for 10 years and with recording in the clinical history of all of them, between 1-01-1990 and 31-12-1994, of the variables required to estimate GFR using the Cockcroft-Gault[8] and MDRD[9] equations and to calculate coronary risk using the original Framingham[16] and the REGICOR[17] equations. In the Cockcroft-Gault equation, GFR was corrected for a body surface area of 1.73 m^2, calculated by the Dubois and Dubois equation.[18] The REGICOR equation was selected because this formula, adapted from the original Framingham equation, has been calibrated and recently validated in a wide sample of the Spanish population.[19] Some equations to calculate risk of cardiovascular death, such as the one derived from the INDANA project,[20] include serum creatinine among the eleven variables used to estimate risk, but this equation has not been validated and its applicability to the Spanish population is unknown. It was therefore not included in this study. Moreover, equations derived from Framingham, despite not including CKD among their risk factors, appear to discriminate adequately the probability of coronary events in patients with this disease.[21]

Cardiovascular events investigated in cohort follow-up included coronary events (acute myocardial infarction and documented angina), stroke, and cardiovascular death (from coronary, cerebrovascular, or other cardiovascular causes). Acceptance of an event as being of cardiovascular origin required confirmation of diagnosis in the specialized setting or at a reference hospital using the relevant tests (stress test, thallium, coronary angiography, etc.). Patients with a high coronary risk were defined as those having a risk $\geq$ 20% in the original Framingham table[16] and $\geq$ 10% in the Framingham-REGICOR tables.[22] Qualified staff completed a case report form for each patient after the following variables were defined: systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol, high density lipoprotein (HDL) cholesterol, smoking, blood glucose, body mass index (BMI), triglycerides, low density lipoprotein (LDL) cholesterol, use of lipid lowering drugs, and use of antihypertensive drugs. CKD was classified in five stages,[6,23] and the term occult CKD was applied when the estimated glomerular filtration rate was less than 60 mL/min (stage 3-5 CKD)[1] with plasma creatinine values < 1.4 mg/dL in males and < 1.3 mg/dL in females.[24] Patients with severe liver disease, morbid obesity (BMI $\geq$ 40 kg/m^2), malnutrition (BMI $\leq$ 18.5 kg/m^2), or limb amputations were excluded.[7] A total of 845 patients (8.3% of the population aged 35-74 years) finally met the inclusion criteria.

Statistical analysis

Data analysis and management was performed using the statistical software SPSS 12.0 for Windows, the R environment (version 2.5.0), and Epi Dat 3.1 software. Parameters used as representative of the sample for the univariate descriptive analysis included mean, standard deviation, observed frequencies, and proportions for normal distributions, and median and quartiles 1 and 3 for non-normal distributions. Normality of variables was verified using a Kolmogorov-Smirnov test and normality diagrams, and homoscedasticity was studied using a Levene test. In the bivariate analysis of normal distributions, a t test for independent samples was used for quantitative variables, and a Chi-square test or a Fisher's exact test for categorical variables. A non-parametric Mann-Whitney U test was used in the bivariate study of variables with a non-normal distribution. A kappa index was used to analyse agreement between the two equations to estimate GFR in diagnosis of occult CKD.[25] Agreement was considered excellent when values ranging from 0.81 and 1 were obtained, good for values ranging from 0.61 and 0.80, and moderate for values ranging from 0.41 and 0.60. For the analysis of the correlation and agreement between the Cockcroft-Gault and MDRD equations as procedures for quantitative measurement of GFR, the Bland-Altman method and the Shapiro-Wilk test were used to assess whether the difference in means was significantly different from zero. Finally, scatter plots, Pearson's correlation coefficient, and the regression line were also obtained.

RESULTS

Table I shows the clinical characteristics of patients included in the cohort. Women represented 56.7% of the sample, and showed a higher rate of occult CKD as compared to men when the MDRD formula was used (17.7% versus 3.6%, $p < 0.001$). Women were also older and showed higher SBP, HDL cholesterol, and BMI values, and a lower coronary risk and proportion of smokers as compared to men (table I). An 8.3% of the population would have CKD using the Cockcroft-Gault formula, and 11.6% using the MDRD equation. Patients diagnosed occult CKD by the Cockcroft-Gault equation were older (67.4 *versus* 64.4 years, $p < 0.001$) and had a greater coronary risk according to both the original Framingham and the REGICOR equations, while patients diagnosed of CKD by the MDRD formula had a higher BMI (29.6 *versus* 26.3 kg/m², $p < 0.001$) and were more commonly women (86.7% versus 67.1%, $p < 0.01$) (table II).

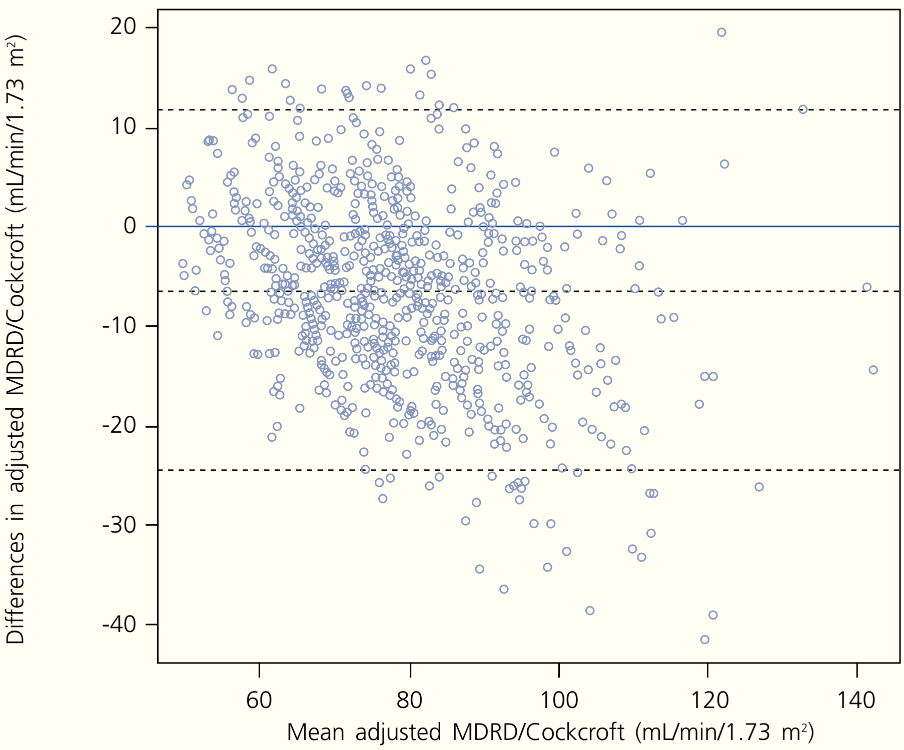
Table I. General characteristics of the study patients

	Total (n = 845)	Females (n = 479)	Males (n = 366)	P
Age (years)	55.5 (9.9)	57.1 (9.3)	53.4 (10.3)	< 0.001
SBP (mmHg)	141.5 (20.8)	143.2 (21.2)	139.3 (20.0)	< 0.01
DBP (mmHg)	85.4 (11.3)	85.3 (10.8)	85.6 (11.9)	0.777
Hypertensive	671 (79.4%)	390 (81.4%)	281 (76.8%)	0.098
Total cholesterol (mg/dL)	242.8 (40.6)	244.7 (39.7)	240.3 (41.7)	0.127
HDL-C (mg/dL)	51.6 (15.1)	56.4 (15.4)	45.3 (12.0)	< 0.001
LDL-C (mg/dL)	164.2 (38.9)	164.7 (38.5)	163.5 (39.6)	0.649
Triglycerides (mg/dL)	117.0 (84.0-162.0)	104.0 (76.0-141.0)	139.0 (99.0-189.0)	< 0.001
Blood glucose (mg/dL)	116.3 (40.3)	115.5 (45.9)	117.4 (31.5)	0.507
Creatinine (mg/dL)	0.967 (0.155)	0.891 (0.121)	1.067 (0.137)	< 0.001
BMI (kg/m²)	28.5 (4.1)	28.7 (4.4)	28.1 (3.5)	< 0.05
Diabetic	197 (23.3%)	105 (21.9%)	92 (25.1%)	0.273
Smokers	207 (24.5%)	45 (9.4%)	162 (44.3%)	< 0.001
Antihypertensive drugs	330 (39.1%)	199 (41.5%)	131 (35.8%)	0.089
Lipid lowering drugs	165 (19.5%)	94 (19.6%)	71 (19.4%)	0.513
Pacientes with GFR by the Cockcroft-Gault equation < 60 mL/min/1.73 m²	70 (8.3%)	47 (9.8%)	23 (6.3%)	0.065
Pacientes with GFR by the MDRD equation < 60 mL/min/1.73 m²	98 (11.6%)	85 (17.7%)	13 (3.6%)	< 0.001
Mean risk in the Framingham-REGICOR equation	6.5% (5.2)	5.2% (3.8)	8.3% (6.1)	< 0.001
Mean risk in the original Framingham equation	16.5% (12.3)	11.9% (8.2)	22.5% (14.2)	< 0.001
Coronary events	84 (9.9%)	33 (6.9%)	51 (13.9%)	< 0.001
Cardiovascular events	107 (12.7%)	47 (9.8%)	60 (16.4%)	< 0.01

Values are given as mean (standard deviation) or number of patients (percentage) in normal distributions, and as median (quartile 1-quartile 3) in non-normal distributions (triglycerides). SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; BMI: body mass index; GFR: glomerular filtration rate; MDRD: abbreviated formula from the Modification of Diet in Renal Disease study.

Table II. Clinical characteristics of patients with occult chronic kidney disease

	Patients with GFR by the MDRD equation < 60 mL/min/1.73 m² (n = 98; 11.6%)	Patients with GFR by the Cockcroft-Gault equation < 60 mL/min/1.73 m² (n = 70; 8.3%)	P
Age (years)	64.4 (6.8)	67.4 (4.7)	< 0.001
Females	85 (86.7%)	47 (67.1%)	< 0.01
SBP (mmHg)	149.7 (21.0)	152.7 (18.5)	0.339
DBP (mmHg)	86.1 (11.3)	83.4 (11.0)	0.125
Hypertensive	77 (78.6%)	56 (80%)	0.974
Total cholesterol (mg/dL)	246.4 (40.8)	249.3 (35.3)	0.632
HDL-C (mg/dL)	53.4 (14.3)	54.7 (15.2)	0.572
LDL-C (mg/dL)	165.6 (39.7)	170.7 (32.7)	0.379
Triglycerides (mg/dL)	119.0 (88.5-156.0)	114.0 (84.0-145.0)	0.164
Blood glucose (mg/dL)	123.1 (41.0)	123.2 (42.1)	0.988
Creatinine (mg/dL)	1.097 (0.101)	1.114 (0.109)	0.300
BMI (kg/m²)	29.6 (4.4)	26.3 (3.5)	< 0.001
Diabetic	32 (32.7%)	21 (30%)	0.844
Smokers	11 (11.2%)	11 (15.7%)	0.536
Antihypertensive drugs	61 (62.2%)	47 (67.1%)	0.624
Lipid lowering drugs	30 (30.6%)	18 (25.7%)	0.633
Mean risk in the Framingham-REGICOR equation	7.5% (4.5)	9.3% (6.5)	< 0.05
Mean risk in the original Framingham equation	17.8% (10.9)	22.8% (15.5)	< 0.05
Coronary events	17 (17.3%)	12 (17.1%)	0.863
Cardiovascular events	22 (22.4%)	16 (22.9%)	0.901



MDRD: Glomerular filtration rate estimated using the abbreviated formula from the Modification of Diet in Renal Disease study.
*Difference between the GFRs estimated using the MDRD and Cockroft-Gault equations, expressed in mL/min and adjusted for a body surface area of 1.73 m².
**Mean GFRs estimated using the MDRD and Cockroft-Gault equations, expressed in mL/min and adjusted for a body surface area of 1.73 m².

Figure 1. Analysis of the correlation between the glomerular filtration rates estimated by the MDRD and Cocokcroft-Gault equations (mL/ min/1.73 m²) using a Bland-Altman plot.

The kappa index of agreement between the two formulas for estimating GFR in diagnosis of occult CKD was 0.55, suggesting a moderate agreement. This conclusion is also drawn by looking at the Bland-Altman plot (fig. 1), where a great number of measurements are seen not to lie around the zero difference ($p < 0.001$). The Pearson's correlation coefficient between the GFRs estimated by the Cockcroft-Gault and the MDRD equations in the whole cohort was 0.828 ($p < 0.001$), and 0.142 ($p = 0.327$) when the relationship was limited to patients with CKD according to both equations. The regression line between both formulas (GFR estimated by the Cockcroft-Gault equation = 4.90 + 1.02 MDRD) suggests that estimation of GFR using the Cockcroft-Gault equation gives higher values than estimated with the MDRD equation; specifically, the Cockcroft-Gault formula tends to give values 4.90 units higher than the MDRD formula.

The number and percentage of patients included in the different intervals of GFR values estimated by both formulas is shown in table III, where agreement between the two formulas is seen to be higher in the lower GFR categories. For instance, 71.4% of the 70 patients with GFR < 60 mL/min/1.73 m^2 using the Cockcroft-Gault equation are included in the same GFR interval in MDRD, while only 43.4% of patients with an estimated GFR ≥ 90 mL/min/1.73 m^2 were included. It is also seen that the Cockcroft-Gault formula usually allocates more patients to higher GFR intervals as compared to the MDRD formula (212 *versus* 108 patients), whereas the MDRD equation assigned a greater proportion of patients to lower GFR categories as compared to the Cockcroft-Gault formula (table III).

To summarize, only 42.4% (50 patients) of the 118 patients considered to have CKD were diagnosed the condition using both formulas. Of the 68 patients diagnosed of occult CKD by only one of the equations, 20 were rated as having occult CKD by the Cockcroft-Gault equation, and 48 by the MDRD formula (fig. 2).

Eighty-four percent of concordant patients (those with occult CKD according to both formulas to estimate GFR, table IV) were women. A low proportion of smokers (10.0%) and a moderate coronary risk according to the original Framingham (18.8%) and REGICOR (7.9%) equations were seen in this female group. A comparison of these patients and discordant patients (those found occult CKD in only one of the equations for estimating GFR) revealed a lower age (64.0 versus 66.7 years, $p < 0.05$) and a higher BMI (29.7 kg/m^2 *versus* 27.2, $p < 0.01$) in the latter group (table IV).

When discordant patient groups were compared to each other, i.e. patients considered to have occult CKD by the Cockcroft-Gault equation versus patients diagnosed CKD by the MDRD formula alone, patients in this second group were seen to be mainly women (89.6%) with obesity (BMI 32.0 kg/m^2) and higher DBP and triglyceride values (table V). By contrast, patients diagnosed occult CKD by the Cockcroft-Gault equation only (table V) were mainly males (75.0%) of an older age (69.1 *versus* 61.9 years, $p < 0.001$) and with a high coronary risk according to both the original Framingham (32.7%) and the REGICOR (13.1%) formulas.

Males showed higher rates of events, both coronary (13.9% versus 6.9% in females, $p < 0.001$) and cardiovascular (16.4% versus 9.8%, $p < 0.01$) during follow-up. However, there were no significant differences in the coronary or cardiovascular event rates between patients diagnosed occult CKD by one or the other formula for estimating GFR (tables I and II).

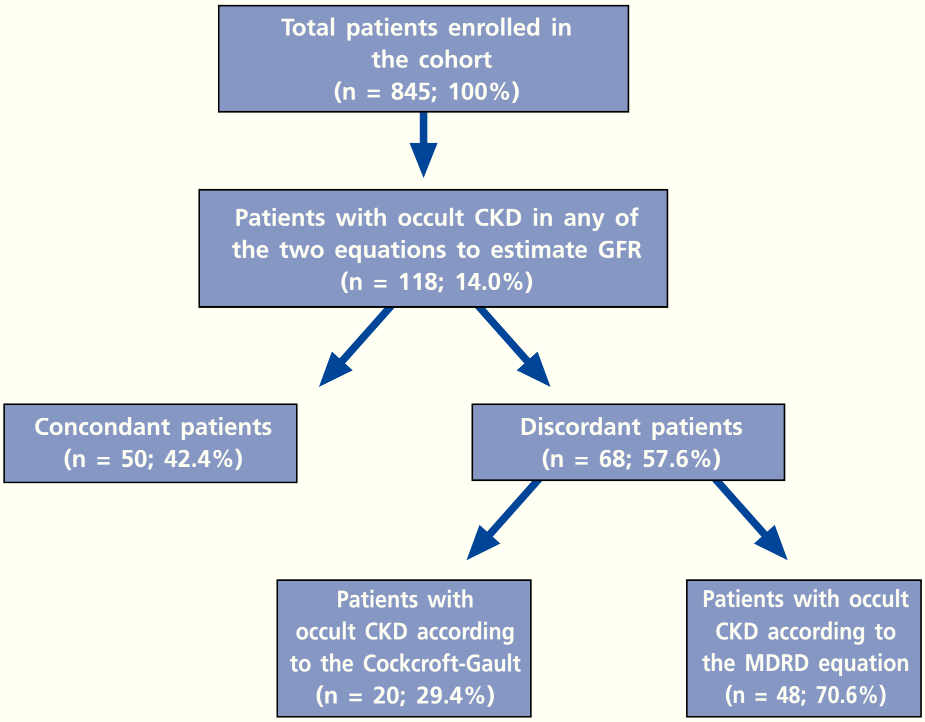
DISCUSSION

CKD is one of the main public health problems due to both its high prevalence[26-28] and its significant cardiovascular morbidity and social and financial costs.[2] The prevalence of occult CKD detected in our population (8.3% and 11.6% using the Cockcroft-Gault and MDRD equations respectively) agrees

Table III. Patient distribution in the different intervals of GFR values (mL/min/1.73 m²) estimated by the Cockcroft-Gault and MDRD equations

GFR estimated by the MDRD equation	GFR estimated by the COCKCROFT-GAULT equation: < 15	[15, 30)	[30, 60)	[60, 90)	> 90	Total
< 15						
[15, 30)						
[30, 60)			**50** **71.4%**	48 8.5%		98 11.6%
[60, 90)			20 28.6%	**499** **88.7%**	120 56.6%	639 75.6%
> 90				16 2.8%	**92** **43.4%**	108 12.8%
Total			70 100.0%	563 100.0%	212 100.0%	845 100.0%

GFR = Glomerular filtration rate (mL/min/1.73 m^2). MDRD: abbreviated formula from the Modification of Diet in Renal Disease study.



CKD: chronic kidney disease
GFR: glomerular filtration rate
MDRD: abbreviated formula from the Modification of Diet in Renal Disease study

Figure 2. Patients with chronic kidney disease according to one or both equations estimating.

Table IV. General characteristics of patients with concordant and discordant diagnosis of occult CKD by the Cockcroft-Gault and MDRD equations to estimate GFR

	Concordant (n = 50)	Discordant (n = 68)	P
Age (years)	66.7 (4.7)	64.0 (7.7)	< 0.05
Females	42 (84%)	48 (70.6%)	0.141
SBP (mmHg)	152.7 (18.6)	148.4 (22.0)	0.266
DBP (mmHg)	83.8 (10.8)	86.8 (11.7)	0.158
Hypertensive	40 (80%)	53 (77.9%)	0.966
Total cholesterol (mg/dL)	248.9 (35.1)	245.8 (43.4)	0.679
HDL-C (mg/dL)	55.2 (14.3)	52.1 (15.1)	0.262
LDL-C (mg/dL)	169.2 (34.3)	165.5 (40.9)	0.605
Triglycerides (mg/dL)	111.0 (77.5-154.0)	124.5 (103.0-149.0)	0.161
Blood glucose (mg/dL)	121.5 (44.5)	125.7 (36.8)	0.576
Creatinine (mg/dL)	1.118 (0.100)	1.084 (0.108)	0.084
BMI (kg/m^2)	27.2 (3.3)	29.7 (5.1)	< 0.01
Diabetic	14 (28%)	25 (36.8%)	0.422
Smokers	5 (10%)	12 (17.6%)	0.336
Antihypertensive drugs	33 (66%)	42 (61.8%)	0.780
Lipid lowering drugs	15 (30%)	18 (26.5%)	0.830
Mean risk in the Framingham-REGICOR equation	7.9% (5.0)	8.8% (6.1)	0.395
Mean risk in the original Framingham equation	18.8% (12.3)	21.4% (14.5)	0.307
Coronary events	8 (16%)	13 (19.1%)	0.846
Cardiovascular events	11 (22%)	16 (23.5%)	0.979

Values are given as mean (standard deviation) or number of patients (percentage) in normal distributions, and as median (quartile 1-quartile 3) in non-normal distributions (triglycerides). SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; BMI: body mass index; MDRD: abbreviated formula from the Modification of Diet in Renal Disease study.

Table V. General clinical characteristics of patients with discordant diagnosis of occult CKD by the Cockcroft-Gault and MDRD equations to estimate GFR

	Patients with CKD according to the Cockcorft-Gault equation (n = 20)	Patients with CKD according to the MDRD equation (n = 48)	P
Age (years)	69.1 (4.3)	61.9 (7.9)	< 0.001
Females	5 (25.0%)	43 (89.6%)	< 0.001
SBP (mmHg)	152.8 (18.8)	146.5 (23.1)	0.285
DBP (mmHg)	82.5 (11.7)	88.6 (11.3)	< 0.05
Hypertensive	18 (90.0%)	37 (77.1)	0.370
Total cholesterol (mg/dL)	250.4 (36.6)	243.8 (46.2)	0.572
HDL-C (mg/dL)	53.3 (17.3)	51.6 (14.3)	0.676
LDL-C (mg/dL)	174.5 (28.4)	161.9 (44.7)	0.170
Triglycerides (mg/dL)	116.0 (94.0-142.0)	129.0 (104.0-161.0)	< 0.05
Blood glucose (mg/dL)	127.7 (36.1)	124.9 (37.4)	0.777
Creatinine (mg/dL)	1.105 (0.132)	1.075 (0.098)	0.304
BMI (kg/m^2)	24.0 (2.6)	32.0 (4.0)	< 0.001
Diabetic	7 (35.0%)	18 (37.5%)	0.935
Smokers	6 (30.0%)	6 (12.5%)	0.169
Antihypertensive drugs	14 (70.0%)	28 (58.3%)	0.530
Lipid lowering drugs	3 (15.0%)	15 (31.3%)	0.279
Mean risk in the Framingham-REGICOR equation	13.1% (8.2)	7.0% (3.9)	< 0.01
Mean risk in the original Framingham equation	32.7% (18.3)	16.7% (9.3)	< 0.001
Coronary events	4 (20%)	9 (18.7%)	0.827
Cardiovascular events	5 (25%)	11 (22.9%)	0.897

Values are given as mean (standard deviation) or number of patients (percentage) in normal distributions, and as median (quartile 1-quartile 3) in non-normal distributions (triglycerides). CKD: chronic kidney disease; SBP: systolic blood pressure; DBP: diastolic blood pressure; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; BMI: body mass index; MDRD: abbreviated formula from the Modification of Diet in Renal Disease study.

with that reported by other studies in our area[27,29-31] and other countries.[32] The greater prevalence of occult CKD in females has also been confirmed by different studies.[29-31] The EROCAP study,[31] conducted in patients seen at primary care centres, found a 7.9% prevalence of occult CKD. This study considered normal plasma creatinine values lower than 1.1 mg/dL in females and 1.2 mg/dL in males and did not exclude patients with extreme BMIs. In our study, if we had disregarded BMI restrictions and accepted the same normal range for plasma creatinine, the occult CKD rate would be 5.7% (with all cases occurring in females). These small differences may be explained by the different mean age and prevalence of cardiovascular risk factors in both populations, with older ages and higher diabetes rates in patients from the EROCAP study. In any case, the prevalence of occult CKD found in the population seen at health centres in both studies could support the need for its early detection in order to decrease the risk of progression and the cardiovascular morbidity associated to CKD.[2] In fact, early identification of CKD in primary care would allow for early intervention on this disease and its risk factors, would facilitate the start of treatment limiting progression of renal damage, and would help avoid use of drugs that impair kidney function, thus reducing the serious social and health implications of CKD.[1] However, the high proportion of hypertensive (66.7%) and diabetic (28.2%) patients enrolled into both the EROCAP study[31] and our own study (including 79.4% and 23.2% of hypertensive and diabetic patients respectively), as well as the mean age in both studies (60.6 and 55.5 years respectively), lead us to question whether screening for occult CKD should maybe not be limited to patients with diabetes or high blood pressure, or older than 55 years, as advocated by other authors until studies showing a better cost-effectiveness ratio in the general population are reported.[33]

Isolated measurement of plasma creatinine is the most universal routine method for assessing kidney function, but its relationship to GFR is poor, particularly in the elderly and especially in females.[26] These data justify the interest of scientific organizations and societies in systematic inclusion of the GFR value, estimated through equations, in routine laboratory reports. The MDRD formula is the best validated equation[34] and the one recommended by the SEN,[7] but other organizations accept use of the Cockcroft-Gault equation to estimate kidney function as an alternative.[35] The lack of standardization of methods to measure creatinine and the characteristics of the populations analysed may explain these disagreements.[36]

Correlation between both equations was low in our study, which represents a significant problem for detection of occult CKD because of the trend to select, at least according to these results, different populations, as has also been previously reported.[14] This dispersion of the values obtained with both equations estimating GFR is not surprising because they are different approaches to the study of kidney function from serum creatinine measurements: the MDRD equation estimates clearance of I^{125} iothalamate, and the Cockcroft-Gault equation estimates creatinine clearance. On the other hand, the presence or absence of weight in one and the other formula may condition results and partly account for the populational differences seen, though in our study values were adjusted for body surface area.[18] However, even if the difference in measurements could be accounted for by the different origin of equations, this explanation would not avoid its implications when the physician has to decide whether or not a given patient should be considered to have renal failure.

The dispersion of values seen in the Bland-Altman agrees with the modest index of agreement between both equations in identification of patients with occult CKD criteria (kappa index of 0.55). All patients from our study with CKD has GFR values ranging from 59 and 30 mL/min/1.73 m^2, i.e. they had stage 3 CKD, the traditionally called renal failure.[5,7] If the MDRD equation is accepted to have a greater diagnostic accuracy[7] for GFR values ranging from 15 and 60 mL/min/1.73 m^2, it could be considered that patients with occult CKD in our study were mainly women (86.7%) with a mean age of 64.4 years, a BMI near to obesity 29.6 kg/m^2), and a moderate coronary risk according to the original Framingham and the REGICOR equations (table III). However, analysis of the discordant groups, i.e. patients defined as having occult CKD by only one of the two equations (table V), provides revealing results. Patients rated as having occult CKD by the MDRD equation only continued to be mainly females (89.6%) with obesity (BMI 32.0 kg/m^2) and a moderate coronary risk. By contrast, patients with occult CKD according to the Cockcroft-Gault equation (table V) were mainly males (75.0%) of an older age (69.1 years), including a high proportion of smokers (30.0%) and diabetics (35.0%), and with a high coronary risk according to both the original Framingham equation (32.7%) and the calibrated REGICOR equation (coronary risk, 13.1%). This patient group, consisting mainly of males, has sufficient cardiovascular risk factors to make biologically likely a high probability of developing CKD. Twenty percent of them experienced a coronary event and 25% some cardiovascular event during 10-year follow-up (table V), which also indirectly suggests that CKD behaves as a significant cardiovascular risk factor at individual level.[21] It is therefore very possible that these are not patients erroneously rated as carriers of occult CKD by the Cockcroft-Gault equation. If the MDRD equation was used in laboratory reports, this would exclude this group of patients who are rated as carriers of occult CKD and with a high true probability of suffering it by the Cockcroft-Gault only, who could be deprived of the measures aimed at slowing CKD progression that the introduction of routine reporting of the estimated GFR intends to promote. These data partly support the recently reported findings of better results with the Cockcroft-Gault equation in patients with advanced CKD (stages 4 and 5).[15] The fact that, in discordant groups, patients rated as having occult CKD by the Cockcroft-Gault equation were mainly males (75%) could also be related to the low proportion of women (4%) enrolled in the original study by these authors.[8] On the other hand, the MDRD equation contains no anthropometric parameters, and it is therefore not surprising that its precision may be different in a population with other anthropometric characteristics despite adjustment for body surface area, with up to 60% of discordant estimates in the elderly population.[37] Our data should encourage, in agreement with recommendation by the SEN[7] and various authors,[36,38] to develop new equations to estimate GFR with a greater diagnostic accuracy from standardized methods to measure creatinine and/or other biological variables, and to validate such equations in independent populations versus reference methods to measure GFR.

Our study has significant limitations. The population enrolled was not selected at random, but based on the availability of a clinical history and the required variables to estimate coronary risk and GFR using the Cockcroft-Gault and MDRD equations. A computerized clinical history system was not available at our centre. However, all clinical records were systematically reviewed and followed up for 10 years, using a tracking and monitoring strategy that prevented missing patients or cardiovascular events. Our results therefore correspond to a population seen in an urban health centre, and may not be extrapolable to the general population, though this has no influence on the comparison of the two equations for GFR estimation analysed. The fact that this study, as the EROCAP study,[31] was based on a single time point, so that patients with a transient kidney function impairment could not be differentiated from those with established CKD, should not influence the comparison either. A significant limitation of the study could be an inadequate identification and quantification of the cardiovascular events occurring during cohort follow-up. However, the methods established for searching and confirming cardiovascular events, consulting clinical records, hospital files, and the registry office, and contacting with relatives were very rigorous. Moreover, it would be difficult that events of this nature were overlooked during a 10-year follow-up. Finally, our study was observational in nature, and the existence of other unidentified confounding factors cannot be completely excluded. Also, and as occurs with this type of studies, its results may only be used to generate new hypotheses.

To summarize, this study confirmed a high prevalence of occult stage 3 CKD (11.6% and 8.3% when the MDRD and Cockcroft-Gault equations are used respectively) in patients aged 35-74 years with no cardiovascular disease. The study also revealed a moderate agreement between the Cockcroft-Gault and MDRD formulas, with a different profile of excluded patients depending on whether one or the other formula is chosen. The choice of the MDRD formula would exclude from diagnosis of CKD a population group consisting mainly of elderly (69 years) males (75%) with a high cardiovascular risk, both estimated by the original Framingham and REGICOR equations and confirmed by 10-year follow-up.

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