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Creatinina sérica y aclaramiento de creatinina para la valoración de la función renal en hipertensos esenciales

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SUMMARY

The shortcoming of serum creatinine (SCr) as an index of renal function is well known, patients can have significantly decreased glomerular filtration rates (GFR) with normal range SCr values, making the recognition of renal dysfunction more difficult. This study was designed to estimate renal function and the prevalence of renal dysfunction in essential hypertensive patients, comparing SCr and 4 formulas used to measure the creatinine clearance (CrCl) (the urinary CrCl formula, Cockcroft-Gault, MDRD and body surface formula)

The study included 721 essential hypertensive patients, 319 men (44.2%), 402 women (55.8%), mean age 56.3 ± 13.9 (53.7 ± 14.4 vs *58.3 ± 13.3). In all subjects SCr was measured and 24-h urine sample was collected to evaluate CrCl. Creatinine clereance was calculated by 4 formulas. Patients were grouped according to age (< 40, 41-65,65-75 and > 76) and renal function was classified as normal when SCr < 1.4 in momen and 1,5 mg/dl in men and CrCl (> 60 ml/m, respectively) within the above written formulas.*

SCr increases with age (1.01 ± 0.36 vs *1.3 ± 1.15) and CrCl decreases according to the 4 formulas (107,6; 92,8; 74,7 and 57,3 for the urinary SCr formula); (117,7; 87,7; 65,9 and 49,5 for the CG formula); (87,4, 74,9, 66,5 and 61 for the MDRD formula) and (97, 85,3, 71,9 and 57,3 for the body suface formula). The 4 formulas are comparable markers of renal function in the overall population. With any formula the percentage of patients with impaired renal function was much higher than indicated by the plasma creatinine alone (4% for SCr)* vs *18,3-25,3% (CrCl < 60 ml/m) according to the 4 formulas. This study documents the substantial prevalence of abnormal renal function in essential hypertension. Estimation of GFR may help to facilitate the early identification of patients with renal impairment.*

Key words: ***Serum creatinin. Renal function. Creatinin clearance.***

CREATININA SÉRICA Y ACLARAMIENTO DE CREATININA PARA LA VALORACIÓN DE LA FUNCIÓN RENAL EN HIPERTENSOS ESENCIALES

RESUMEN

La creatinina plasmática puede subestimar el filtrado glomerular. Los pacientes pueden tener una disminución significativa del filtrado glomerular con

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un valor de creatinina plasmática dentro de la normalidad, haciendo difícil la detección precoz del deterioro de la función renal. En este trabajo se estima la función renal así como la prevalencia de la disfunción renal en pacientes con hipertensión arterial esencial, mediante la determinación de creatinina sérica, comparándolo con la medida del aclaramiento de creatinina, medida por 4 fórmulas distintas; la fórmula habitual con recogida orina de 24 h, la fórmula de Cockcroft-Gault, MDRD abreviada y la fórmula habitual corregida por la superficie corporal. El estudio incluye 721 hipertensos esenciales, 319 hombres (44,2%), 402 mujeres (55,8%), con edad media 56,3 ± 13,9 (53,7 ± 14,4 vs *58,3 ± 13,3). En todos ellos se determina la creatinina plasmática así como el aclaramiento de creatinina por las 4 fórmulas señaladas. Los pacientes fueron agrupados en función de la edad, en 4 grupos (< 40, 41-65, 65-75 y > 76 años), la función renal fue calificado como normal cuando la creatinina sérica es <1,4 y < 1,5 mg% en mujeres y hombres y el aclaramiento > 60 ml/m en las cuatro fórmulas.*

La creatinina plasmática aumenta con la edad (1,01 ± 0,36 vs *1,3 ± 1,15 en aquellos con edad menor de 40 y mayor de 70 años y el aclaramiento de creatinina disminuye con la edad según las 4 fórmulas (107,6; 92,8; 74,7, 57,3 para la fórmula habitual); (117,7; 87,7; 65,9; 49,5 para la fórmula de Cockroft-Gault); (87,4, 74,9, 66,5 y 61 para la fórmula MDRD abreviada) y (97, 85,3, 71,9; 57,3 para la fórmula de superficie corporal). Las 4 fórmulas son comparables para la medición de la función renal, con cualquiera de ellas, el porcentaje de deterioro de la función renal fue mucho mayor (18,3-25,3% (CrCl < 60 ml/m) que el obtenido cuando se utiliza la creatinina plasmática (4%). Este estudio, demuestra la importancia de la determinación del aclaramiento de creatinina en hipertensos esenciales a la hora de valorar el filtrado glomerular, detectando más precozmente el deterioro de la función renal que cuando se utiliza la creatinina sérica.*

Palabras clave: ***Creatinina sérica. Función renal. Aclaramiento de creatinina.***

INTRODUCTION

The annual increase rate of patients initiating renal replacement therapy is 6-8%. The estimation for the United States is an increase from 300,000 patients in 1999 to near 651,000 by the year 2001.[1] This increase is due to several factors, the longer longevity and the greater presence of cardiovascular pathology, especially hypertension and diabetes mellitus. These patients use a great amount of resources, and the magnitude of the problem is such that the National Kidney Foundation in the USA has proposed an action plan that allows for detecting renal disease, estimating its prevalence, and developing an action and prevention plan.[2]

The two leading causes of chronic renal failure and entry into a regular dialysis program in Spain are type 2 diabetes mellitus and arterial hypertension, highly present in elderly patients. Many of them are referred late to nephrology departments and many start replacement therapy within their first nephrology visit.[3,4]

A false assessment of glomerular filtration rate (GFR) could explain this very late referral to dialysis. In many patients, renal function assessment is done through plasma creatinine determination, a parameter that does not reflect the same renal function level in all patients for being influenced by several factors such as age, gender, race, body surface area, type of diet, and use of certain drugs.[5-11] To avoid these limitations, it is necessary to turn to creatinine clearance, which reflects more accurately glomerular filtration rate and may detect early renal function worsening, even before raising of creatinine levels. Today, there are alternative formulas to measure creatinine clearance to the one used by collecting 24-hour urine, based on an indirect estimate from serum creatinine, age, gender, and weight. The most frequently used ones are Cockcroft-Gault' formula[12] and the MDRD[13] formula, which may even be more accurate.[14] There have been numerous reports validating these formulas.[15]

The importance of measuring clearance is not only because of a better renal function assessment but also to detect early patients that considered normal by using plasma creatinine determination.[9,11]

There are controversies about the incidence of renal impairment in hypertensive patients, from a mild impairment,[16,17] to a 5% from the MRFIT study.[18] In Spain, data range from 12.3% according to Aranda[19] to 33% in the Valdecilla-Santander Group,[10,20] and 40% according to Olivares.[21]

The aim f this study was to assess renal function by plasma creatinine levels and compare them with that obtained by creatinine clearance determination measured through four different formulas, in a group of patients with essential hypertension.

MATERIAL AND METHODS

Seven hundred and twenty-one patients that were referred to the Hypertension Unit were studied. All patients with secondary arterial hypertension were excluded. All patients were studied according to the usual protocol, with clinical history, physical examination, anthropomorphic data, and clinical investigations that included full blood count, fundus examination, EKG or echocardiogram, abdominal ultrasound, and studies required to rule out secondary arterial hypertension.

Creatinine was determined by Jaffé' s reaction. Creatinine clearance was calculated by four different formulas:

- Usual formula: CrCl: [Diuresis (urine/24h) × urine Cr (mg/dL)] × [1440 × plasma Cr (mg/dL)].
- Cockcroft and Gault formula: [(140 - age (years)) × Weight (kg)] × [plasma Cr (mg/dL) × 72] , for male patients. And the same formula bur multiplying by 0.85 for female patients.
- Abbreviated MDRD formula[22]

$$186 \times Cr^{-1.154} \times age^{-0.203} \times (0.742 \text{ if female and/or } 1.210 \text{ if Afro-American})$$

- Creatinine clearance by body surface area: [urine Cr (mg/dL) × urine vol. (mL) × 1.73] ÷ [plasma Cr (mg/dL) × 1.440 × body surface area] Where GFR = CrCl: creatinine clearance (mg/min).
  Cr: creatinine (mg/dL)

Data were analyzed by the SPSS version 11.5 statistical software.

In order to relate creatinine with the different clearances, the non-parametric Spearman's correlation coefficient has been used, together with the corresponding graph to visualize that relationship. In order to assess whether the different creatinine clearance formulas yield similar results, a linear regression has been applied having as a reference the creatinine clearance formula corrected by body surface area.

Results are expressed as mean _ standard deviation for continuous variables and as percentages for qualitative variables. P values < 0.05 have been considered as being statistically significant.

RESULTS

Of the 721 patients studied, 44.2% (319) were male and 55.8% (402) were female. Age ranged from 13-85 years, with a mean age of 56.3 ± 13.9 (53.7 ± 14.4 for men vs. 58.3 ± 13.3 for women).

Table I depicts the patients' data on anthropometrical characteristics and plasma creatinine and creatinine clearance values, categorized by gender, observing statistically significant differences in all studied parameters.

Figure 1 depicts the graph representation of the relationship between plasma creatinine and creatinine clearance. All four curves follow a hyperbolic pattern, the MDRD formula being the most characteristic.

Figure 2 depicts the correlation coefficient (R^2) for the three formulas (usual formula, Cockcroft and Gault formula, and MDRD formula) having a reference the usual formula corrected by body surface area. There is a linear relationship with all of them, with an r value ranging from 0.830 for Cockcroft and Gault formula (p<0,001), 0.862 (MDRD) (p < 0,001), and 0.976 (usual formula) (p < 0,001).

Table II shows plasma creatinine and creatinine clearance values with all the formulas used in the study, and segregated by gender. Female patients show slightly lower values than male patients, both for plasma creatinine (0.91 ± 0.21 versus 1.12 ± 0.26) and creatinine clearance by the different formulas.

Table III depicts the data for creatinine clearance by age, into four groups (<40, 40-65, 66-75, >75 years). Independently of the formula used, the greater the age the lower creatinine clearance. The highest clearance corresponds to the group of hypertensive patients younger than 40, and the lowest to those aged > 75 years; these values are statistically significant.

Table I. Anthropomorphic values, plasma creatinine and creatinine clearance of all studied patients

	N	Minimum	Maximum	Mean	SD
Age	721	13	90	56.32	13.988
Height	721	1.14	174.00	4.2664	20.49385
Weight	721	37.0	177.0	75.964	14.6993
IBM	721	.00	60.02	28.9932	6.26058
Plasma Cr	720	.50	2.40	1.0089	.26255
Usual formula	720	.73	298.18	88.5941	40.74452
Cockroft and Gault formula	720	14.65	233.54	84.6059	29.95306
MDRD formula	720	22.55	151.02	73.8933	18.08978
Formula based on body surface	720	.70	271.96	82.1919	37.61966
Valid N (according to list)	720				

The percentage of hypertensive patients with impaired renal function (sCr ≥ 1.5 in men and ≥ 1.4 mg% in women) was 4% (5.7% men; 2.7% female patients). When creatinine clearance is used as a measurement of renal function, we see that the percentage of hypertensive patients with impaired renal function (creatinine clearance ≤ 60 ml/min) ranges from 18.3% with the CG formula up to 25.3% with the body surface area formula. With the MDRD formula and the 24-h formula the percentage was 19.6% and 23.2%, respectively (fig. 3).

The percentage of hypertensive patients with plasma creatinine levels within the normal range but with creatinine clearance values lower than 60 mL/min was 15.4, 16.2, 21.0 and 22.6%, by the different formulas (Cockcroft and Gault, MDRD, usual formula, and the formula corrected by body surface area, respectively).

To determine the effect of body weight on plasma creatinine and creatinine clearance levels, we divided the studied patients into those with body weight higher or lower than 80 kg (table IV). Plasma creatinine is slightly lower in those with lower weight (0.98 ± 0.2 *vs* 1.00 ± 0.26), with no significant differences by gender. When using the usual formula, creatinine clearance is lower in hypertensive patients with lower weight, but once corrected for body surface area, the difference by weight vanishes off,

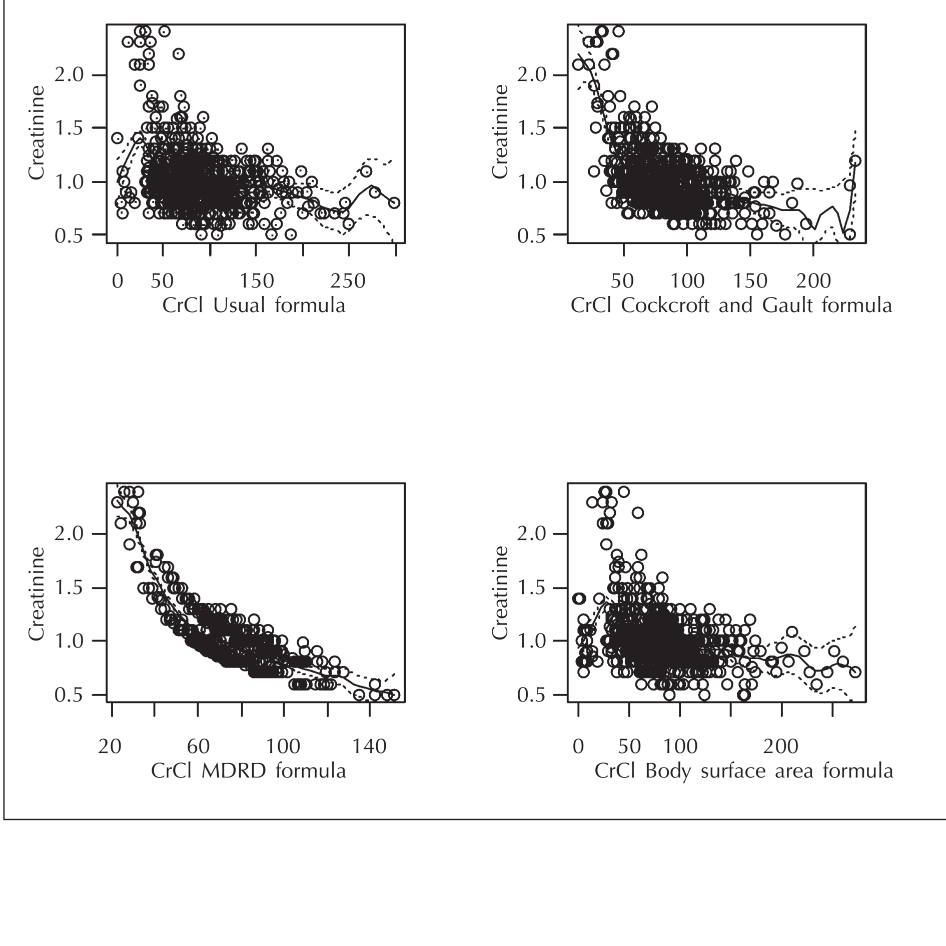

Fig. 1.—Graph representation of the relationship between plasma creatinine and creatinine clearance for all studied patients.

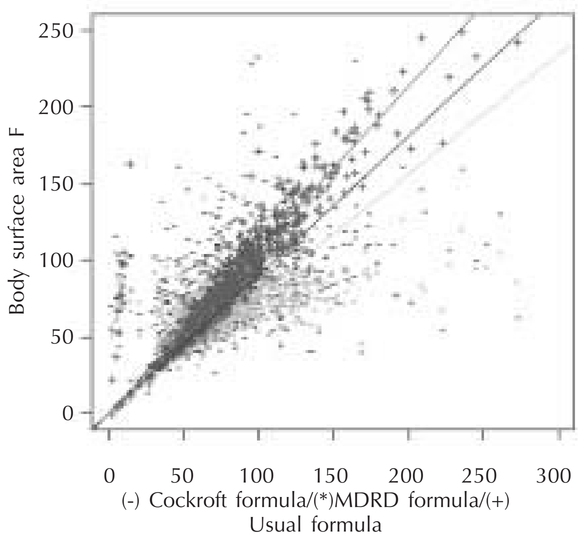

Fig. 2.—Correlation coefficient between creatinine clearance by the usual formula corrected by body surface are and the three other formulas.

Table II. Plasma creatinine and creatinine clearance values according to the four used formulas

	Gender	N	Mean	Standard deviation	Standard error of the mean
Plasma Cr	Male	318	1.1269	.26508	.01486
	Female	402	.9156	.21974	.01096
Usual formula	Male	318	97.7589	42.62788	2.39045
	Female	402	81.3444	37.69391	1.88000
Cockroft and Gault formula	Male	318	91.4475	30.80023	1.72719
	Female	402	79.1938	28.14699	1.40384
MDRD formula	Male	318	76.9966	17.91369	1.00455
	Female	402	71.4384	17.87146	.89135
Formula based on body surface area	Male	318	85.0778	37.26893	2.08994
	Female	402	79.9091	37.78495	1.88454

which indicates that body surface area is more important than weight. There are no differences with the MDRD formula, since it does not include weight, and the Cockcroft and Gault formula overestimates clearance by not including the height.

When we divided patients by BMI, those with a BMI < 30 had higher plasma creatinine, although not statistically significant, and lower creatinine clearance, only significant by the usual formula and the Cockcroft and Gault formula, but not with MDRD or body surface area formulas (table V).

Table III. Creatinine clearance by age groups with the four used formulas

		N	Mean	Standard deviation	95% confidence interval for the mean	
					Lower limit	Upper limit
Usual formula	≤ 40 years	99	107.6864	50.47761	97.6188	117.7540
	41-65 years	414	92.8006	39.35258	88.9988	96.6025
	66-75 years	163	74.7506	31.96851	69.8060	79.6953
	≥ 76 years	44	57.3415	22.17825	50.5987	64.0843
	Total	720	88.5941	40.74452	85.6130	91.5753
Cockroft and Gault formula	≤ 40 years	99	117.7626	38.18448	110.1468	125.3783
	41-65 years	414	87.7647	22.80700	85.5613	89.9680
	66-75 years	163	65.9023	18.69159	63.0113	68.7934
	≥ 76 years	44	49.5698	12.54029	45.7572	53.3824
	Total	720	84.6059	29.95306	82.4143	86.7974
MDRD formula	≤ 40 years	99	87.4246	18.13034	83.8086	91.0406
	41-65 years	414	74.9002	16.17442	73.3376	76.4628
	66-75 years	163	66.5785	17.82333	63.8217	69.3352
	≥ 76 years	44	61.0712	14.51698	56.6576	65.4848
	Total	720	73.8933	18.08978	72.5697	75.2168
Formula based on body surface area	≤ 40 years	99	97.0145	43.17864	88.4027	105.6264
	41-65 years	414	85.3254	36.99082	81.7517	88.8991
	66-75 years	163	71.9308	33.15723	66.8024	77.0593
	≥ 76 years	44	57.3705	22.38111	50.5660	64.1750
	Total	720	82.1919	37.61966	79.4394	84.9444

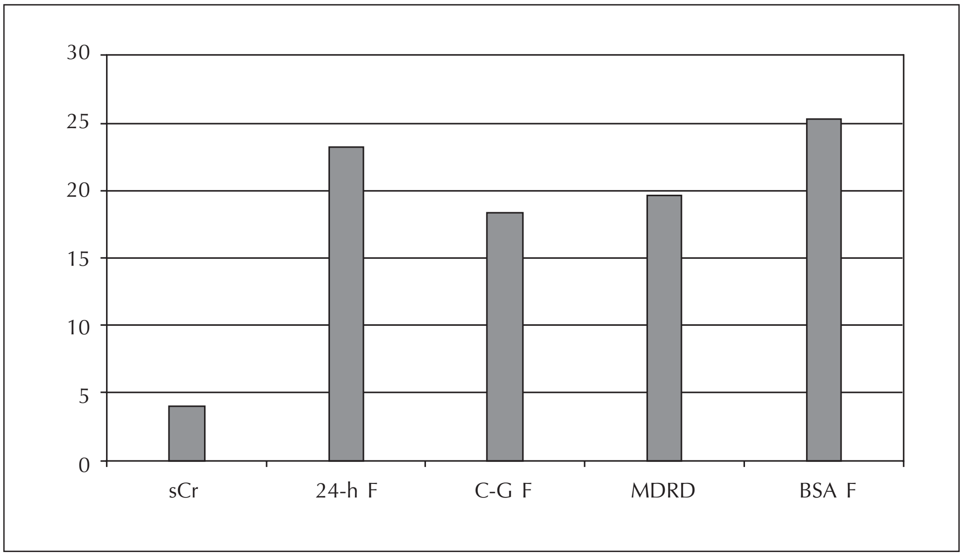

Fig. 3.—Percentage of patient with renal dysfunction (increase of plasma creatinine and decrease of creatinine clearance by the 4 formulas).

Table IV. Plasma creatinine and creatinine clearance values by weight

	Weight	N	Mean	Standard deviation	Standard error of the mean
Plasma Cr	Weight < 80 kg	476	.9825	.25712	.01179
	Weight ≥ 80 kg	244	1.0606	.26585	.01702
Usual formula	Weight < 80 kg	476	81.8728	36.96005	1.69406
	Weight ≥ 80 kg	244	101.7063	44.50444	2.84910
Cockroft and Gault formula	Weight < 80 kg	476	74.7737	22.54192	1.03321
	Weight ≥ 80 kg	244	103.7867	33.20509	2.12574
MDRD formula	Weight < 80 kg	476	73.2115	18.09111	.82920
	Weight ≥ 80 kg	244	75.2232	18.05009	1.15554
Formula based on body surface area	Weight < 80 kg	476	81.0498	37.39082	1.71381
	Weight ≥ 80 kg	244	84.4201	38.04045	2.43529

DISCUSSION

Data from these study of patients with essential arterial hypertension show that creatinine clearance is a much more reliable parameter for renal function study, especially in elderly patients. In many of these patients, renal function determination is done through plasma creatinine determination. The percentage of patients with renal function impairment widely varies when the determination is done through plasma creatinine determination or by creatinine clearance.[8-10,23]

Glomerular filtration rate may be measured by several means. Although there are no ideal markers for measuring glomerular filtration, the most appropriate is inulin clearance. Inulin has a major drawback, which is that it is an exogenous substance that must be perfused to calculate clearance, which absolutely limits its clinical application. In ordinary clinical practice, glomerular filtration rate is measured through endogenous creatinine clearance. Creatinine is derived from skeletal muscle metabolism and daily

Table V. Plasma creatinine and creatinine clearance values by BMI

	BMI > 30	N	Mean	Standard deviation	Standard error of the mean
Plasma Cr	NO	419	1.0175	.26782	.01308
	YES	301	.9969	.25499	.01470
Usual formula	NO	419	85.4275	38.70931	1.89107
	YES	301	93.0021	43.09826	2.48414
Cockroft and Gault formula	NO	419	77.4922	24.76681	1.20994
	YES	301	94.5083	33.56378	1.93458
MDRD formula	NO	419	74.4997	18.37267	.89756
	YES	301	73.0492	17.68417	1.01930
Formula based on body surface area	NO	419	83.1510	37.59442	1.83661
	YES	301	80.8569	37.67663	2.17165

meat intake, and it is eliminated from circulation at a constant rate, its plasma levels remaining constant, as well. In steady state conditions, creatinine excretion is equal to creatinine production, so that plasma creatinine levels vary inversely to glomerular filtration rate.

Plasma creatinine as expression of glomerular filtration has got its limitations, since a decrease in glomerular filtration only leads to a slight increase in plasma creatinine since its tubular excretion increases; so, a slight increase in plasma creatinine does not necessarily means that glomerular filtration is normal. But a plasma creatinine increase > 2 mg/dL makes excretion process to become saturated and starts to reflect glomerular filtration.[24] In our study, we wanted to assess renal function by plasma creatinine and by creatinine clearance in patients with essential hypertension for early detection of renal dysfunction.

The relationship between plasma creatinine and glomerular filtration follows a parabolic curve, which shows how a serious function impairment, measured by creatinine clearance, is not translated into an increase of plasma creatinine levels. So, an increase in plasma creatinine indicates an already important loss of glomerular filtration. This is a rather relevant issue in the clinical practice, where the general practitioner relies preferably on plasma creatinine values for measuring renal function, forgetting creatinine clearance. The use of certain drugs, such as NSAIDS, ACEIs, or ARA-II, may induce renal function impairment or irreversible renal failure.[25,26]

The use of plasma creatinine by the general practitioner is due to the difficulty in measuring creatinine clearance, especially if the patient has to collect a 24-hour urine sample. Indirect methods to measure creatinine clearance have shown to be very accurate.[10,12,13,23,27] Our results confirm this good relationship between direct and indirect methods of measuring creatinine clearance.

Renal creatinine clearance calculated by any of the formulas used in our study, and taking into account their limitations for certain age or gender groups, reflects better renal function than plasma creatinine value, since the percentage of patients showing a renal function impairment measured by these formulas is greater than that observed when using plasma creatinine values. We observed that indirect methods for renal function measurement through plasma creatinine and anthropometrical measurements correlate very well with creatinine clearance corrected by body surface area, so that they may be replaced in clinical practice without any disadvantage. We may state that the Cockcroft-Gault formula and the MDRD formula are the best indicated as an indirect measurement of creatinine clearance.

We have seen significant differences by gender between creatinine clearance by the usual method and by Cockcroft and Gault formula, but not with the other two formulas. These differences may be due to body weight, higher in men. Those with a body weight > 80 kg have significantly greater plasma creatinine and creatinine clearance levels, both in men and women, with the usual formula and with the Cockcroft and Gault formula.

Patient's weight has an influence in creatinine clearance determination, so that in those patients with lower weight creatinine clearance will be lower for the same value of plasma creatinine, as compared to those with heavier weight. Taken altogether, gender, weight, and age must be taken into account when evaluating renal function since they are not usually considered in daily clinical practice.

Our results also confirm that with normal creatinine values, creatinine clearance may be less than 60 mL/min, up to 22.6%, more important in the elderly and in women. This percentage is lower than that found by Fresnedo,[10] reaching 57% in the elderly; these differences may be explained because they use an abnormal value for creatinine clearance, being < 50 mL/min. Duncan *et al.*[28] find by the Cockcroft and Gault formula a creatinine clearance less than 50 mL/min in 47.3% of patients aged > 70 years and in 12.6% in those aged 60-69 years. We believe that these differences may be related to the formula used, patients' age, and the clearance value used as being pathological.

Although the initial purpose was not to determine the percentage of hypertensive patients with renal function impairment, we do have observed that the percentage of patients with essential hypertension showing renal dysfunction varies depending on the use of plasma creatinine (4%) or creatinine clearance (up to 21%). These differences may partially explain the controversies regarding the incidence of chronic renal failure in arterial hypertension. The MRFIT study[18] sets at 5% the incidence rate using plasma creatinine. In Spain, Aranda *et al.*[19] report figures of 12.3% and F. Fresnedo[10] finds renal dysfunction in 33% of patients using a limit value < 50 mL/min for creatinine clearance by the Cockcroft and Gault formula. Olivares *et al.*[21] find up to 40% of hypertensive patients showing a creatinine clearance less than 60 mL/min, especially in those older than 75 years. Likely these differences may be related to the parameter used to define renal function and to age of studied patients. DOQI guidelines[2] state that any subject with GFR < 60 mL/min/1.73 m^2 for longer than 3 months should be classified as having chronic renal failure, independently of no objective renal damage.

This study is done using the correlation between plasma creatinine and four different methods to find creatinine clearance in patients with essential hypertension. Most of the studies establish their correlations using clearance by the Cockcroft and Gault formula.[29-32] Creatinine clearance using this latter formula is lower with increasing age, so that for a given plasma creatinine value glomerular filtration rate may vary more than 50% depending on patient's gender and age. Gender, age, and body weight are known factors that should be considered in renal function assessment, a consideration not sufficiently applied in clinical practice.[10] Serum creatinine increase is a poorly sensitive indicator of GFR decrease; many patients with GFR decrease will have serum creatinine values within the normal range.[6,10,13,15,20]

Renal creatinine clearance calculated by any of the formulas used in our study, taking into account their limitations for certain age and gender groups, reflect better renal function than plasma creatinine value since the percentage of patients showing renal function impairment measured through these formulas is much higher than that using plasma creatinine values. We observed that indirect methods for renal function measurement by plasma creatinine levels and anthropometrical measurements correlate very well with creatinine clearance normalized by body surface area, so that they may be replaced in clinical practice with no disadvantages. Creatinine clearance calculated by the Cockcroft and Gault formula and by the usual formula the most appropriate ones in male patients, with no significant differences in female patients.

The keystone to prevent renal failure-associated complications is precisely to know the renal function degree. The usual assessment though plasma creatinine determination may be insufficient since we have observed that normal plasma creatinine values may correspond, in many cases, to renal failure. The possibility of having available methods for creatinine clearance methods without having to use cumbersome methodologies, such as 24-hour urine collection, may contribute to do a better clinical assessment than with plasma creatinine alone. Today, we have the availability of other methodologies to determine plasma creatinine, such as cystatin determination, which might be a more accurate value than plasma creatinine for renal function assessment.[33-36]

We all should make an effort trying to implement the true knowledge of renal function and step forward to early referral of renal failure patients to Nephrology Departments. The presence of nephrologists in Primary Care Centers, with the bond to be determined at the appropriate time, would have very positive consequences on quality of care and on issues (educational and financial) related to late care.

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