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Renal function and cardiovascular risk in patients with primary arterial hypertension. FRESHA study

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SUMMARY

Background: *In the past few years there has been a growing amount of information about renal dysfunction and cardiovascular risk. The objectives of this study were to assess the prevalence of renal dysfunction and evaluate the relation between renal function and cardiovascular risk in patients with essential hypertension.*

Methods: *A multicenter, cross-sectional survey of unselected patients with essential hypertension attending primary care settings in Spain was performed between june and november 2004. Renal function was evaluated with the abbreviated equation of the Modification of Diet in Renal Disease study. Renal insufficiency was defined as an estimated glomerular filtration rate < 60 ml/min/1.73 m^2.*

Results: *Eighty-eight investigators from 50 centers recruited 2,130 patients being mean age 65.6 +/- 11 years and female 53%. Prevalence of diabetes, lipid abnormalities, and previous cardiovascular disease were 30.3%, 45.9%, and 42.1% respectively. Prevalence of renal insufficiency was 32.4% (95% CI 30.4-34.4). Patients suffering from renal insufficiency showed a higher prevalence of cardiovascular disease when comparing with those with an estimated glomerular filtration rate = or > 60 ml/min/1.73 m^2 (56.2%* vs *35.3%, OR 2.35, 95% CI 1.95-2.82, p < 0.001). A logistic regression analysis showed that the relation of renal dysfunction with cardiovascular disease was independent of other variables or classical cardiovascular risk factors as age, female sex, diabetes, smoking, hypercholesterolemia, and systolic blood pressure.*

Conclusions: *Renal insufficiency was present in 32.4% of patients with essential hypertension attending primary care settings. Cases with renal dysfunction showed a higher cardiovascular risk. Hypertensive patients with renal insufficiency should be considered as candidates for an aggressive approach of cardiovascular risk management.*

Key words: ***Essential hypertension. Renal disease. Cardiovascular risk. Estimated renal function.***

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FUNCIONAL RENAL Y RIESGO CARDIOVASCULAR EN PACIENTES CON HIPERTENSION ARTERIAL. ESTUDIO FRESHA

RESUMEN

Introducción: *Se ha descrito una relación entre el descenso del filtrado glomerular y el riesgo cardiovascular. Los objetivos de este estudio fueron verificar si la función renal es un marcador independiente de riesgo cardiovascular en casos con HTA esencial y estimar la prevalencia de insuficiencia renal en estos pacientes.*

Métodos: *Estudio multicéntrico, observacional y transversal realizado en 50 centros de Atención Primaria de España por 88 investigadores. Cada médico incluyó de modo consecutivo 25 pacientes con HTA esencial no seleccionados. Se estudiaron datos demográficos, factores de riesgo cardiovascular, comorbilidad vascular y utilización de fármacos cardioprotectores. La función renal fue determinada por la concentración de creatinina sérica y mediante el filtrado glomerular estimado según la ecuación abreviada del estudio Modification of Diet in Renal Disease (MDRD). La insuficiencia renal se definió por un filtrado glomerular < 60 ml/min/1,73 m^2.*

Resultados: *Se estudiaron 2.130 individuos con una edad media de 65,6 ± 11 años, 53% mujeres. El 68,4% de los pacientes tenía PA ≥ 140/90 mmHg. La prevalencia de insuficiencia renal fue 32,4% (IC 95% 30,4-34,4). La prevalencia de enfermedad cardiovascular fue más elevada en los casos con insuficiencia renal (56,2%* vs *35,3%, OR 2,35; IC 95% 1,95-2,82, p < 0,001). En el análisis de regresión logística múltiple se verificó que esta relación fue independiente del resto de factores (sexo, edad, diabetes mellitus, tabaquismo, hipercolesterolemia y presión arterial sistólica). El uso de agentes antihipertensivos, estatinas y antiagregantes plaquetarios fue mayor en los pacientes con insuficiencia renal.*

Conclusiones: *Uno de cada 3 pacientes con HTA esencial seguidos en Atención Primaria presentó insuficiencia renal. Los casos con insuficiencia renal presentaron un riesgo cardiovascular más elevado que aquellos con función renal más conservada. Los pacientes hipertensos con disfunción renal podrían ser candidatos al manejo terapéutico que se aplica a otros grupos de alto riesgo cardiovascular.*

Palabras clave: ***Hipertensión arterial. Enfermedad renal. Riesgo cardiovascular. Función renal estimada.***

INTRODUCTION

The relationship between primary arterial hypertension (AHT) and renal disease had low consideration in classic epidemiological studies analyzing the relationship between blood pressure (BP) level and vascular pathology. In recent years, several studies on hypertensive patients have shown that low renal function is associated with a greater cardiovascular risk.[1-3] These data have allowed for the recognition, for the first time ever, in seventh report of the *Joint National Committee* that glomerular filtration rate (GFR) > 60 mL/min is a major cardiovascular risk factor.[4] This association is not surprising since vascular involvement and the acceleration of AHT-associated atherosclerosis is universal and cannot be circumscribed, as has been usually considered, to the territories of the heart coronary and cerebral arteries. AHT-associated renal involvement is known as nephrosclerosis.[5] It has been proven that there is an negative relationship between renal function level and the severity of cardiovascular disease.[6]

Serum creatinine level is by itself an error source when calculating renal function. Individuals with reduced muscle mass, such as the elderly, especially of female gender, may show serum creatinine levels within accepted normal ranges and still have severely compromised renal function. Calculating renal function by means of 24-hour urine creatinine clearance may also be a source for error due to diffi-

culties in urine collection. Recent guidelines of the *National Kidney Foundation*[7,8] propose to determine renal function by means of equations based on serum creatinine, gender, weight, and age, such as the Cockcroft and Gault formula[9] or the simpler abbreviated equation from the *Modification Diet of Renal Disease* (MDRD)[10] study. Besides being a vascular risk marker, the presence of reduced GFR may be useful for early detection of renal failure and the implementation of therapeutic measures to slow its progression.

There are few studies about the prognostic value of GFR level or serum creatinine levels in patients with primary AHT. None of them has formulated this problem in a prospective way. With *post hoc* analysis, it has been shown that renal function decrease is independently associated with greater cardiovascular risk.[1-3,11]

The aim of the this study was to verify whether renal function may be an independent cardiovascular risk factor in patients with primary AHT. Other goals were to know the prevalence of renal failure within this population and assessing the degree of usage of cardio- and renoprotective medication in patients with and without GFR decrease.

Subjects and Methods

This is a multicenter, cross-sectional, and observational study performed at primary health care and national level. Each participating physician (n = 88) consecutively included the 25 first patients with primary AHT attending their office for two weeks. The sample size is justified for 90% prevalence of greater risk of associated cardiovascular disease, with a maximum error of 13% and a confidence level of 95%. The study protocol was approved by the Clinical Investigation Ethics Committee of Central University Hospital of Asturias.

Patients aged ≥ 40 years with primary AHT giving their informed consent to participate were included. Excluded patients were those with secondary AHT, associated disabling disease (cancer, dementia, etc.), intercurrent acute disease during the assessment period, and pregnancy. Data were gathered between April and December of 2004. Registered variables and the corresponding definitions are summarized in Table I. Renal failure was defined depending on the following parameters: serum creatinine level ≥ 1.2 mg/mL in women and ≥ 1.3 mg/mL in men, or estimated GFR < 60 mL/min/1.73 m^2 by means of the abbreviated equation of the MDRD study[10] or the Cockcroft-Gault[9] formula corrected for 1.73 m^2 of body surface area.

Statistical Analysis

Generated data were refined and registered at a centralized unit. Qualitative variables are presented as frequency distribution and 95% confidence interval. The prevalence of dependent variables was done based on age, gender, and presence or absence of several cardiovascular risk factors and associated comorbidity. Quantitative variables are described as mean value, standard deviation (SD), range and 95% confidence interval. The association between qualitative variables was assessed by the c^2 test. The effect of each of independent variable on quantitative variables was assessed by Student's t test (by comparing one variable with two categories) or by analysis of variance (ANOVA). Then, a multiple logistic regression model was created with those variables having a significant relationship with the degree of renal function decrease in the bi-variant analysis. Calculations were done with SPSS 12.0 software.

RESULTS

Data from 2230 patients were collected of which 2130 were appropriate for evaluation. One hundred patients (4.5%) were cleared because of incomplete data. Basal characteristics of studied individuals are shown in table II. This is an advanced-age population, with a preponderance of female gender, and high rate of cardiovascular risk factors and associated vascular comorbidity. Controlled BP with levels < 140/90 mmHg was seen in 36.1% of the cases, this figure being 17.3% in those patients with glomerular filtration rate < 60 mL/min/1.73 m^2 (MDRD). A total of 421 individuals had renal failure by elevated serum creatinine levels (19.8% prevalence; 16.1-21.5). According to estimated GFR by the abbreviated MDRD equation 691 cases (32.4% prevalence; 30.4-34.4) and by Cockcroft-Gault 's formula 730 patients (34.5% prevalence; 32.5-36.5) had renal failure. The interclass correlation coefficient between GFR estimated by the abbreviated MDRD equation and GFR calculated by the Cockcroft-Gault 's formula was 0.87 (0.86-0.88).

Patients with estimated (MDRD) GFR < 60 mL/min/1.73 m^2 as compared to those with GFR ≥ 60 mL/min/1.73 m^2 had older age, more frequency of female gender, higher systolic BP level, and higher prevalence of diabetes and associated cardiovascular disease (56.2 % vs. 35.3, % ($p < 0.001$) (Table III). Categorization of GFR into four decreasing stages allowed verifying a negative correlation between GFR and each one of the cardiovascular events, as well as with global cardiovascular morbi-

Table I. Study variables. Definitions

Variable	Definición
VITAL STATISTICS	
Age	Current age at assessment time
Gender	Male or female
CARDIOVASCULAR RISK FACTORS	
Arterial hypertension	BP levels ≥ 140/90 mmHg or being treated; BP was measured according to SEH-LELHA guidelines[13]
Diabetes	Previous diagnosis according to ADA criteria[12] or being on dietary, oral anti-diabetics, or insulin therapy.
Hypercholesterolemia	Total cholesterol levels ≥ 240 mg/dl in previous 6 months or being on treatment with diet or hypolipidemic agents
Lipid profile	Total cholesterol, HDL-cholesterol, triglycerides and LDL-cholesterol levels calculated by the Friedewald's formula in previous 6 months
Smoker	Smoking (cigarettes, cigars or pipe) within the last month
Obesity	Body mass index ≥ 30 kg/m^2
WELL-ASCERTAINED VASCULAR COMORBIDITY (HOSPITAL ADMISSION OR REPORT FROM A SPECIALIST)	
Ischemic heart disease	Angor pectoris of any kind, myocardial infarction, or coronary grafting or stent.
Cerebrovascular disease	Previous episode of sudden reversible or irreversible neural deficit or asymptomatic lesions in imaging tests
Heart failure	Hospital admission due to heart failure episode
Peripheral arteriopathy	Intermittent claudication or ankle/arm index ≤ 0.9; carotid arteries stenosis
Left ventricular hypertrophy	EKG changes: Sokolow or Cornell's indexes, or T wave inversion in D1-aVL or V5-V6 leads
Atrial fibrillation	Complete and chronic arrhythmia due to atrial fibrillation at EKG
RENAL FUNCTION ASSESSMENT	
Serum creatinine (mg/dL)	Determination by the method of Jaffé's kinetic reaction in previous 6 months
GFR estimated by the MDRD formula[10] (mL/min/1.73 m^2)	186.3 × (serum creatinine)$^{-1.154}$ × age $^{-0.203}$ ¥ 0.742 for women × 1.21 if Afro-American
CrCl estimated by Cockcroft-Gault formula[9] (mL/min/1.73 m^2)	[(140 – age) × weight / (serum creatinine × 72)] × 0.85 for women and corrected for body surface area (BSA) of 1.73 m2 according to DuBois' formula[14] [BSA (m^2) = 0.20247 × height (m) $^{0.725}$ × weight (kg) $^{0.425}$]

BP, blood pressure; SEH-LELHA, Spanish Society of Hypertension – Spanish League for fighting against arterial hypertension; ADA, *American Diabetes Association*; EKG, electrocardiogram; GFR, glomerular filtration rate; MDRD, *Modification of Diet in Renal Disease*; CrCl, creatinine clearance.

dity (figures 1 and 2). The degree of AHT control to BP levels < 140/90 mmHg was similar in those cases with or without renal failure (32.7% vs. 31%, p = 0.41).

The logistic regression analysis included possible confounding factors (age, gender, diabetes, hypercholesterolemia, smoking history, and systolic BP) and showed that the relation between renal failure and cardiovascular disease was independent (*odds ratio* 2.31, 95% CI 1.88-2:84) (Table IV).

Those cases with GFR < 60 mL/min/1.73 m^2 received higher number of antihypertensive medications with higher usage, as well, of statins and platelet anti-aggregants (table V).

Table II. General characteristics of the sample

Variable	
N	2.130
Age (years)	65.6 ± 11.0
Female gender n (%)	1.136 (53.3)
Systolic BP (mmHg)	145.4 ± 16.3
Diastolic BP (mmHg)	83.6 ± 9.9
BP < 140/90-mmHg n (%)	673 (31.6)
Diabetes n (%)	645 (30.3)
Hypercholesterolemia n (%)	977 (45.9)
Smokers n (%)	348 (16.3)
Obesity * n (%)	785 (36.9)
Creatinine (mg/dL)	1.00 ± 0.30
Estimated GFR † (mL/min/1.73 m^2)	70.2 ± 21.1
Elevated creatinine ‡ n (%)	421 (19.8)
Estimated GFR † < 60 mL/min/1.73 m^2 n (%)	691 (32.4)
Ischemic heart disease n (%)	352 (16.5)
Cerebrovascular disease n (%)	159 (7.5)
Heart failure n (%)	185 (8.7)
Peripheral arteriopathy n (%)	223 (10.5)
Left ventricular hypertrophy n (%)	393 (18.5)
Atrial fibrillation n (%)	138 (6.5)
At least one cardiovascular disease § n (%)	896 (42.1)

BP, blood pressure, GFR, glomerular filtration rate.
* Body mass index ≥ 30 kg/m^2.
† GFR estimated by the abbreviated equation of the Modification of Diet in Renal Disease (MDRD) study.[10]
‡ Serum creatinine ≥ 1.2 mg/dL for women or ≥ 1.3 mg/dL for men.
§ Any of the previously mentioned (ischemic heart disease, cerebrovascular disease, heart failure, peripheral arteriopathy, left ventricular hypertrophy or atrial fibrillation).

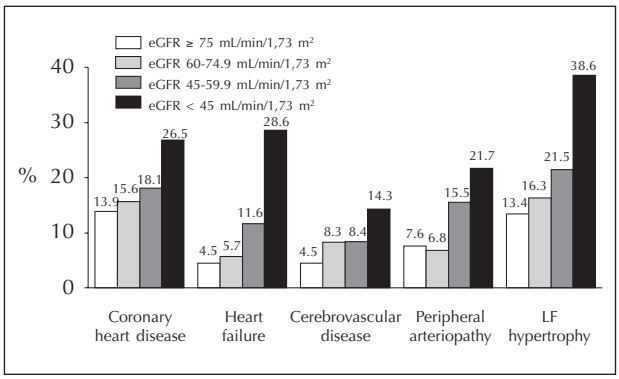

Fig. 1.—Prevalence of several kinds of cardiovascular diseases by different stages of estimated glomerular filtration rate. * Estimated glomerular filtration rate by the abbreviated equation of the Modification of Diet in Renal Disease (MDRD) study.10 LV, left ventricle; eGFR, estimated glomerular filtration rate.*

DISCUSSION

This is the first study published in Spain showing that renal failure is an independent risk factor for cardiovascular disease in patients with primary AHT followed at the primary care setting. Other Spanish studies had analyzed renal failure prevalence in pa-

Table III. Comparison between patients with renal failure (eGFR* < 60 mL/min/1.73 m^2) and without renal failure (eGFR* ≥ 60 mL/min/1.73 m^2)

Variable	eGFR* < 60 mL/min/1,73 m^2	eGFR* ≥ 60 mL/min/1,73 m^2	p / OR (IC 95% CI), p
N	691	1.439	
Age (years)	69.3 ± 10.4	63.8 ± 10.9	< 0.001
Female gender n (%)	503 (72.8)	633 (44)	3.41 (2.80-4.15), < 0.001
SBP (mmHg)	146.7 ± 17.3	144.8 ± 15.9	0.013
DBP (mmHg)	83.7 ± 10.3	83.6 ± 9.7	0.86
Diabetes n (%)	239 (34.6)	406 (28.2)	1.34 (1.11-1.63), 0.003
Hypercholesterolemia n (%)	331 (47.9)	646 (44.9)	1.13 (0.94-1.35), 0.19
Smokers n (%)	68 (9.8)	280 (19.5)	0.45 (0.34-0.60), < 0.001
Obesity † n (%)	272 (39.4)	513 (35.6)	1.17 (0.97-1.41), 0.09
CHD n (%)	141 (20.4)	212 (14.7)	1.49 (1.18-1.89), < 0.001
CVA n (%)	69 (10.0)	90 (6.3)	1.66 (1.20-2.31), 0.002
CHF n (%)	112 (16.2)	73 (5.1)	3.62 (2.65-4.94), < 0.001
PA n (%)	119 (17.2)	104 (7.2)	2.67 (2.02-3.54), < 0.001
LVH n (%)	181 (26.2)	212 (14.7)	2.05 (1.64-2.57), < 0.001
AF n (%)	81 (11.7)	57 (4.0)	3.22 (2.26-4.58), < 0.001
CVD ‡ n (%)	388 (56.2)	508 (35.3)	2.35 (1.95-2.82), < 0.001
Number of CVD § n (%)	1.02 ± 1.13	0.52 ± 0.82	< 0.001

eGFR, estimated glomerular filtration rate ; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; CVA, cerebrovascular accident; CHF, congestive heart failure; PA, peripheral arteriopathy; LVH, left ventricular hypertrophy; AF, atrial fibrillation; CVD, cardiovascular disease.
* GFR estimated by the abbreviated equation of the Modification of Diet in Renal Disease (MDRD) study.[10]
‡ Any of the previously mentioned (ischemic heart disease, cerebrovascular disease, heart failure, peripheral arteriopathy, left ventricular hypertrophy or atrial fibrillation).

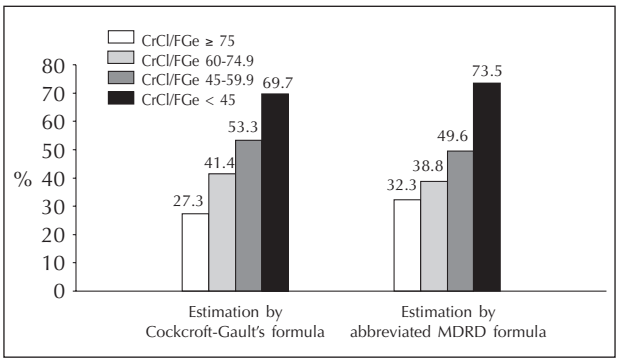

Fig. 2.—Prevalence of cardiovascular disease by different stages of creatinine clearance or estimated glomerular filtration rates. * CrCl, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease study.*

Table IV. Data from multiple logistic regression analysis of the influence of estimated glomerular filtration rate (eGFR)* < 60 mL/min/1.73 m^2 on cardiovascular disease controlling other risk factors

Variable	OR (95% CI)	p
eGFR * < 60 mL/min/1.73 m^2	2.31 (1.88-2.84)	< 0.001
Age	1.04 (1.03-1.05)	< 0.001
Male gender	1.93 (1.57-2.37	< 0.001
Diabetes	1.52 (1.25-1.86)	< 0.001
Smoking history	0.96 (0.73-1.27)	0.78
Hypercholesterolemia	1.60 (1.33-1.93)	< 0.001
Systolic blood pressure	1.00 (0.99-1.01)	0.61

* GFR estimated by the abbreviated equation of the Modification of Diet in Renal Disease (MDRD) study.[10]

Table V. Usage of cardio- or renoprotective agents in patients with and without renal failure (eGFR* < 60 mL/min/1.73 m^2 and eGFR* ≥ 60 mL/min/1.73 m^2)

	eGFR* < 60 ml/min/1,73 m^2	eGFR* ≥ 60 ml/min/1,73 m^2	OR (95% IC); p
N	691	1439	
Number of anti-hypertensive agents	1.61 ± 0.78	1.49 ± 1.15	0.021
ACEI or ARA-II n (%)	419 (60.6)	887 (61.6)	0.96 (0.80-1.15); 0.65
Beta-blockers n (%)	85 (12.3)	210 (14.6)	0.82 (0.63-1.07); 0.15
Statins n (%)	299 (43.3)	557 (38.7)	1.21 (1.01-1.45); 0.04
Platelet anti-aggregants n (%)	197 (28.5)	325 (24.5)	1.23 (1.01-1.51), 0.04

eGFR, estimated glomerular filtration rate; ACEI, angiotensin II converting enzyme inhibitors; ARA-II, angiotensina II receptor antagonists.
* GFR estimated by the abbreviated equation of the Modification of Diet in Renal Disease (MDRD) study.[10]

tients with primary AHT,[15,16] but the possible link between decreased renal function and cardiovascular risk was not studied. The present work shows that in primary arterial hypertension patients even low decreases in renal function are associated to greater vascular risk, and that the relationship between GFR decrease and vascular co-morbidity progressively increased from values lower than 75 mL/min/1.73 m^2, as has been cited in other studies.[17]

Several *post hoc* analyses done within the last 5 years and based on data from large epidemiological studies of high risk patients[17-21] and in some population-based study such as the one in San Francisco area, in California,[22] have shown that renal failure, defined as estimated GFR < 60 mL/min, is an independent cardiovascular risk factor as powerful as other well known factors such as diabetes, systolic BP, or left ventricle hypertrophy. The mechanisms by which renal failure may promote cardiovascular disease are not well understood but it has been clearly demonstrated that both diseases share risk factors (age, diabetes, AHT, hypercholesterolemia, and smoking) and that some factors specific to renal failure, such as anemia or calcium-phosphorus metabolism impairment, also favor vascular disease.[23]

In recent years, there is a tendency to consider chronic renal disease as a "valvulopathic" process in which, similarly to diabetes, there is an aggregation of vascular risk factors.

The studies analyzing the relationship between renal function and cardiovascular morbimortality in hypertensive populations are scant. PIUMA[2] and Syst-China[3] studies showed that serum creatinine level was an independent cardiovascular risk marker. Similarly to our study, Ruilope *et al.*[1] in the HOT study, showed that patients with GFR < 60 mL/min had higher systolic BP, older age, higher frequency of female gender, higher prevalence of myocardial infarction and ictus. Soon after, Leoncini *et al.*[11] showed in their study on 358 cases of young (mean age

47 years) untreated hypertensive cases that 18% had GFR < 60 mL/min. Renal dysfunction was related to age, BP level, LDL-cholesterol level, and cigarette smoking. In a later study that included 957 never treated patients, the same authors verified that renal function, estimated by the Cockcroft–Gault 's formula, had a negative correlation with systolic BP level and with LDL-cholesterol level, and that patients in the lowest quintiles of GFR had higher prevalence of left ventricle hypertrophy.[24] Very recently, in their prospective study on 9929 hypertensive patients followed for 9.6 years, Hailpern *et al.*[25] showed that there was a negative correlation between estimated GFR and mortality due to ischemic heart disease.

Hypertensive population represents an important load in primary care clinics. The presence of renal failure manifested by decreased GFR or by the presence of microalbuminuria entails an additional vascular risk. The present study shows, similarly to mentioned works, that hypertensive individuals with renal failure had older age, higher systolic BP, and higher diabetes prevalence. These three are important risk factors and may explain by themselves the higher percentage of vascular disease. However, the logistic regression model that included these and other risk factors showed that renal failure was by itself an independent risk factor for cardiovascular morbidity.

It has been cited several times that serum creatinine level is an inadequate parameter for measuring renal function, especially in the elderly.[26] It is better to determine renal function through estimated GFR by the MDRD abbreviated equation of by Cockcroft-Gault' s formula adjusted by body surface area.[8] Data analysis was done using both formulas, but MDRD was preferred because of being more accurate and being recommended in elder patients, as the ones of our sample.[27,28] Besides, it is easier to perform since its determination can easily be done automatically by clinical biochemistry laboratories since patient's weight is not necessary. Even though, a comparison between both methods was done by using the interclass correlation coefficient (ICC) in order to check its fitness level. The outcomes showed that both methods had an ICC value close to 0.9, which indicates an excellent fit and, theoretically, there should be no differences when using one method or the other. Similarly to other studies,[1,18] we found renal failure prevalences considerable higher to those obtained when using serum creatinine levels, 34.5% and 32.4% with Cockcroft-Gault and MDRD formulas, respectively, and 19.8% with creatinine values. These prevalence data are higher than those described in population-based studies[22,29], although in those studies mean age was considerably lower. In a study by Olivares *et al.*[16] done at our country on 2249 hypertensive patients with mean age of 69.5 years, there were prevalence data slightly higher: 40.4% of their patients had GFR < 60 mL/min (Cockcroft–Gault, not corrected for 1.73 m2 of body surface area). The differences seen between prevalences using serum creatinine level and standardized formulas may reflect the important number of people with occult renal failure, with the implications on clinical management of these patients.[30] These difference has already been reported in a study done in our country on type 2 diabetes mellitus patients, the authors highlighting the need to use this type of standardized formulas in Primary Care.[31]

The higher number of antihypertensive medications used by patients with GFR < 60 mL/min/1.73 m^2 might be justified by the presence of a higher percentage of cardiovascular disease, and also because BP control (especially systolic BP) is more difficult in elder patients. The same reasons might be given for the higher consumption of statins and antiaggregants. However, it is striking the low usage of cardioprotective drugs such as beta-blockers, and the lack of any difference between patients with and without renal failure by use of specifically renoprotective agents such as renin-angiotensin system blockers.[32]

Our study has some limitations that should be pointed out. The high number of participating investigators may favor the occurrence of data gathering errors; however, the large sample size contributes to lessen the importance of this issue. The other limitation lies in the lack of centralization of serum creatinine determination at just one laboratory, which may introduce certain degree of variability, but since the determination technique is well standardized (Jaffé's kinetic reaction) it is likely that this circumstance will be not so relevant. We should also point out that renal function determination by the indicated formulas has been very little tested in individuals such as those in the present work, with normal renal function or only slightly decreased.[26]

To conclude, calculation of estimated GFR by using standardized formulas should be a usual practice at the offices of physicians caring for patients with primary AHT, since they may detect a higher risk population requiring closer follow-up and management. It is likely that primary AHT-associated renal function should be considered as goal for secondary prevention. However, longitudinal and prospective studies would be needed to verify the data from this cross-sectional study.

APPENDIX

List of participating physicians at the FRESHA study, by alphabetic order

L. C. Abajo, A. C. Aguado, M. A. Alba, E. Álvaro, J. M. Arche, M. J. Barreda, J. Bayo , A. Benet , J. Blanco, R. Bofill, R. Cervantes, A. Cumplido, J. M. de Eugenio, F. del Moral, V. del Rosario, I. Domingo, D. Domínguez, M. Duran, C. Escudero, J. Farré, M. Fernández Fernández, J. Fernández Torrente, P. Flórez, J. E. Forcada, J. Gabas, V. García Abad, P. García Álvarez, A. García Lerín, J. M. García Polón, V. Gasull, I. Gil, B. González López, V. Guirao, J. A. Hernández, E. Hevia, I. Hortelano, J. Insúa, J. D. Jorques, V. López, E. Llopis, A. Macías, P. Marco, C. Marín, F. Martín, F. Medina, D. Mejías, J. A. Montiu, S. Montserrat, J. M. Navarrete, J. J. Navarro, A. Ortega, J. M. Ortí, C. Pérez Linares, M. Pizarro, B. Poyatos, M. A. Prieto, J. Prieto, J. Rama, J. M. Ramírez, B. Rebes, P. Rey, R. Ribelles, M. Robles, J. Rodríguez, R. Ruiz, E. Sánchez Carrión, I. Sánchez Hernández, S. Suárez, J. P. Tobalina, E. Tortosa, S. Tranche, L. A. Vara, C. Varela, M. D. Vargas, M. T. Ventura, J. C. Zamorano, J. F. Zuazagoitia.

REFERENCES

1. Ruilope LM, Salvetti A, Jamerson K, Hansson L, Warnold I, Wedel H y cols.: Renal function and intensive lowering of blood pressure in hypertensive participants of the hypertension optimal treatment (HOT) study. *J Am Soc Nephrol* 12: 218-25, 2001.
2. Schillaci G, Reboldi G, Verdecchia P: High-normal serum creatinine concentration is a predictor of cardiovascular risk in essential hypertension (The PIUMA Study). *Arch Intern Med* 161: 886-91, 2001.
3. Wang JG, Staessen JA, Fagard RH, Birkenhäger WH, Gong L, Liu L y cols.: Prognostic significance of serum creatinine and uric acid in older Chinese patients with isolated systolic hypertension. *Hypertension* 37: 1069-74, 2001.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL y cols.: Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 42: 1206-52, 2003.
5. Gorostidi M, Marín R: Nefropatía vascular. Concepto y significado. Epidemiología. Hipertensión arterial esencial e insuficiencia renal. Nefroesclerosis, nefropatía isquémica o aterosclerótica. *Nefrología* 24 (Supl. 6): 73-83, 2004.
6. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL y cols.: Kidney Disease as a Risk Factor for Development of Cardiovascular Disease. A statement from the American Heart Association councils on kidney in cardiovascular disease, high blood pressure research, clinical cardiology, and epidemiology and prevention. *Circulation* 108: 2154-69, 2003.
7. National Kidney Foundation Guideline. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 39 (Supl. 1): S1-S266, 2002.
8. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW y cols.: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 139: 137-47, 2003.
9. Cockroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31-41, 1976.
10. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease study group. *Ann Intern Med* 130: 461-70, 1999.
11. Leoncini G, Viazzi F, Parodi D, Vettoretti S, Ratto E, Ravera M y cols.: Mild renal dysfunction and subclinical cardiovascular damage in primary hypertension. *Hypertension* 42: 14-8, 2003.
12. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 27 (Supl. 1): S5-10, 2004.
13. Marín R, De la Sierra A, Armario P, Banegas JR, Campo C, Gorostidi M: Guía sobre el diagnóstico y tratamiento de la hipertensión arterial en España. *Med Clin (Barc)* 125: 24-34, 2005.
14. DuBois D, DuBois EF: A formula to estimate the approximate surface area if height and weight be known. *Arch Intern Med* 17: 863-71, 1916.
15. Aranda P, Ruilope LM, Marín R, Aljama P, Luque M: Estudio transversal sobre prevalencia de insuficiencia renal en la hipertensión arterial esencial. Estudio *Laennec*. *Nefrología* 15: 134-40, 1995.
16. Olivares J, Guillén F, Sánchez JJ, Morales FJ: Influencia de la presión arterial y la edad en la función renal. Estudio «Cuidar el riñón». *Nefrología* 23: 137-44, 2003.
17. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL y cols.: Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 351: 1285-95, 2004.
18. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134: 629-36, 2001.
19. Weiner DE, Tighiouart H, Stark PC, Amin MG, MacLeod B, Griffith JL y cols.: Kidney disease as a risk factor to recurrent cardiovascular disease and mortality. *Am J Kidney Dis* 44: 198-206, 2004.
20. Ronald MA, Kostense PJ, Bos G, Dekker JM, Nijpels G, Heine RJ y cols.: Mild renal insufficiency is associated with increased cardiovascular mortality: HOORN Study: *Kidney Int* 62: 1402-7, 2002.
21. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C y cols.: Cardiovascular mortality risk in chronic kidney disease: comparison of traditional and novel risk factors. *JAMA* 293: 1737-45, 2005.
22. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalisation. *N Engl J Med* 351: 1296-305, 2004.
23. Clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 45 (Supl. 3): S1-S153, 2005.
24. Leoncini G, Viazzi F, Parodi D, Ratto E, Vettoretti S, Vaccaro V, y cols.: Creatinine clearance and signs of end-organ damage in primary hypertension. *J Hum Hypertens* 18: 511-6, 2004.
25. Hailpern SM, Cohen HW, Alderman MH: Renal dysfunction and ischemic heart disease mortality in a hypertensive population**.** *J Hypertens* 23: 1809-16, 2005.
26. Swedko PJ, Clark HD, Paramsothy K, Akbari A: Serum creatinine is an inadequate screening test for renal failure in elderly patients. *Arch Intern Med* 163: 356-60, 2003.
27. Froissart M, Rossert J, Jacquot C, Paillard M, Houillier P: Predictive performance of the modification of diet in renal disease and Cockcroft-Gault equations for estimating renal function. *J Am Soc Nephrol* 16: 763-73, 2005.

28. Verhave JC, Fesler P, Ribstein J, du Cailar G, Mimran A: Estimation of renal function in subjects with normal serum creatinine levels: influence of age and body mass index. *Am J Kidney Dis* 46: 233-41, 2005.
29. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS: Prevalence of chronic kidney disease and decreased kidney function in the adults US population: third national health and nutrition examination survey. *Am J Kidney Dis* 41: 1-12, 2003.
30. Gallego E, Lopez A, Lorenzo I, Lopez E, Llamas F, Illescas ML y cols.: Referencia precoz y tardía al nefrólogo; su influencia en la morbimortalidad en hemodiálisis. *Nefrología* 23: 234-42, 2003.
31. Tranche S, Riesgo A, Marín R, Díaz González G, García Fernández A: Prevalencia de insuficiencia renal «oculta» en población diabética tipo 2. *Aten Primaria* 35: 359-64, 2005.
32. Gorostidi M, Marín R: Tratamiento de la hipertensión arterial en pacientes con insuficiencia renal. Estadios 2 y 3 de la enfermedad renal crónica. *Nefrología* 24 (Supl. 6): 91-100, 2004.