Underestimation of renal risk in cardiology clinics. RICAR study

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SUMMARY

Aims: *The aim of this study was to assess the rate of patients attended in cardiology outpatient clinics in whom microalbumine or glomerular filtration rate had been determined, at least once, in the previous 12 months.*

Methods: *It was an observational, transversal, multicentric study. 1,224 patients were included from 124 centers in Spain. Epidemiological, anthropometric, analytic and electrocardiographic data were recruited. Glomerular filtration rate was calculated thereafter by means of the simplified equation of the MDRD.*

Results: *Microalbumine was determined in 34% of the patients, of those 49% had positive microalbumine. Microalbumine rates were higher in patients with diabetes, heart failure, atrial fibrillation, peripheral artery disease or serum creatinine levels > 1.3 mg/dl. However, only young patients, diabetics and those with left ventricular hypertrophy had this exam performed more often. The glomerular filtration rate was determined in 11% of the patients. 30% of the population had moderate or severe renal dysfunction (filtration rate < 60 ml/min) and only 21% of the population hat normal renal function (filtration rate > 90 ml/min). Glomerular filtration rate was assessed more frequently in patients with serum creatinine > 1.3 mg/dl and those with history of heart failure.*

Conclusions: *The prevalence of renal dysfunction in hypertensive patients attended in Cardiology clinics is high. However, the methods recommended for early detection of renal dysfunction are scarcely used by cardiologists. These figures do not improve significantly in high risk patients.*

Key words: *Glomerular filtration rate. Microalbuminuria. Arterial hypertension. Vascular risk.*

RESUMEN

Objetivos: **El objetivo del estudio fue evaluar la proporción de pacientes hipertensos atendidos en consultas de cardiología cuya microalbuminuria y/o tasa de filtrado glomerular se había determinado al menos una vez en los últimos 12 meses.**

Métodos: **Se trata de un estudio observacional, transversal, multicéntrico. Incluyó a 1.224 pacientes hipertensos de 124 centros en España. Se recogieron datos epidemiológicos, antropométicos, analíticos y electrocardiográficos. El filtrado glomerular se calculó a posteriori mediante la ecuación simplificada de MDRD.**

Resultados: **La microalbuminuria se determinó en un 34% de pacientes, de ellos el 49% tenía microalbúmina positiva. Las tasas de microalbúmina fueron superiores en diabéticos, pacientes con antecedentes de insuficiencia cardiaca, fibrilación auricular, enfermedad arterial periférica o cifras de creatinina sérica > 1,3 mg/dl. Sin embargo esta prueba solo se realizó con más frecuencia en pacientes jóvenes, diabéticos y en aquellos con hipertrofia ventricular izquierda. El filtrado glomerular se calculó por su médico en el 11% de los pacientes. El 30% de los pacientes del estudio tenía disfunción renal en grado moderado o severo (filtrado < 60 ml/min) y solo el 21% tenía función renal normal (filtrado > 90 ml/min). El filtrado glomerular se calculó con más frecuencia en pacientes con creatinina sérica > 1,3 mg/dl y aquellos con antecedentes de insuficiencia cardiaca.**

Conclusiones: **Existe una elevada prevalencia de disfunción renal en hipertensos vistos por cardiólogos. Sin embargo, las técnicas recomendadas para la detección precoz de disfunción renal están infrautilizadas entre los cardiólogos. Estas cifras no mejoran sustancialmente entre subgrupos de alto riesgo.**

Palabras clave: Filtrado glomerular. Microalbuminuria. Hipertensión arterial. Riesgo vascular.

INTRODUCTION

Renal function abnormalities are associated with high cardiovascular risk. This increased risk has been shown for all ranges of renal failure, not only for patients with end-stage renal failure, but also for those with a mild or moderate reduction in glomerular filtration rate (GFR)[1,2] or with increased urinary albumin excretion or microalbuminuria (MAU).[3-5] As a result of these findings, the major international societies recommend in their clinical guidelines that the presence of positive MAU or an estimated GFR < 60 ml/min be considered as a major cardiovascular risk factor.[6-8]

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Simple and sensitive methods have now been developed for detecting renal function abnormalities. Determination of MAU allows the detection of target organ damage and indicates the presence of microcirculation impairment, as well as permitting the monitoring of treatment and the choice of drug therapy.[9] GFR is the best method for measuring overall renal function. The use of formulas such as the one derived from the Modification in Diet in Renal Disease (MDRD) Study[10] or the one proposed by Cockcroft and Gault[11] allows a more precise approximation of renal function than a single determination of serum creatinine or creatinine clearance, while also reducing the technical complications and discomfort for the patient compared to clearance.[12] The renal function assessment, in addition to its interest for stratifying the cardiovascular and renal risk of the patients, has important implications for their follow-up and treatment.

Arterial hypertension and other forms of clinical presentation of cardiovascular disease are closely linked to the development of chronic renal disease, and play a key role in the development, clinical course and subsequent management of this disease. Determination of renal function is mandatory for risk stratification and the therapeutic approach to hypertensive patients. There are no studies to date assessing whether determination of renal function is performed adequately in clinical practice in hypertensive patients. The primary aim of this study was to assess the proportion of patients attended in cardiology outpatient clinics in whom MAU and/or GFR had been determined at least once in the previous 12 months. As a secondary aim, it sought to determine the association of these renal markers with cardiovascular risk factors and cardiovascular morbidity.

MATERIALS AND METHODS

Design

This was an observational, cross-sectional, retrospective, multicenter study. There was no drug intervention. The study was carried out in 1,224 hypertensive patients recruited consecutively in cardiology outpatient clinics. A total of 124 centers in Spain participated in the study. Each investigator included a total of 10 patients, who were the last 10 patients seen in the clinic with a diagnosis of arterial hypertension who met the inclusion criteria and none of the exclusion criteria. The inclusion criteria were patients age 18 years or over and a confirmed diagnosis of arterial hypertension. The exclusion criteria were patients with known renal disease with serum creatinine > 2.0 mg/dl, hospitalized patients, and patients with a life expectancy < 3 months. The study was approved by the Independent Ethics Committee of Hospital Universitario de San Juan.

Data collection

The following data were collected using a questionnaire: age, sex, weight, height, history of arterial hypertension, diabetes, dyslipidemia, smoking, obesity, sedentarism, presence of cardiovascular diseases or family history of cardiovascular disease. In addition, anthropometric measures were taken including height, weight, body mass index and abdominal circumference. Obesity was considered as a body mass index of 30 kg/m^2 or greater. The presence of left ventricular hypertrophy was defined according to Sokolow-Lyon electrocardiographic criteria (voltage sum SV1+RV5 or RV6 > 35 mm). Biochemical data were obtained from the last laboratory test performed in the 6 months prior to collection of the study data. Determination of MAU and determination or calculation of GFR and the method used for each was assessed. Blood pressure was taken according the standard guidelines with a mercury sphygmomanometer. After the patient had remained seated for 5 minutes, 3 blood pressure measurements were taken each 2 minutes apart. The average of the last 2 measurements was obtained and considered the patient's blood pressure.

Statistical analysis

Continuous variables was expressed as mean ± standard deviation and compared using Student's *t* test for unpaired data or the Welch test if the homocedasticity of the variances was significantly different. Normality of the distribution was checked using stem and leaf plots. Categorical variables were expressed as percentage of the study population and compared with the X^2 test.

In the case of MAU, since it was a variable not calculable a posteriori, the analyses were performed based on the values provided by the investigators. In the case of GFR, the analyses were performed from the values calculated with the MDRD equation, which allowed the analysis of 87% of patients versus 11% of patients with GFR provided by the investigator.

Logistic regression models were adjusted to explain the variables independently associated with the active search for renal dysfunction. The adjusted odds ratios (OR) and their 95% confidence intervals (CI) are presented. Variables with proven clinical relevance and those with a significance level in the univariate analysis < 0.1 were included.

In all hypothesis contrasts, the null hypothesis was rejected with a type 1 or α error of < 0.05. The analysis was performed using the SPSS version 13 statistical package.

RESULTS

Patients

The mean age of the sample was 67 ± 10 years, and 40% of patients were women, 34% were diabetics and 59% were dyslipidemic. The baseline characteristics of the study population are shown in table I.

Determination of microalbuminuria

Microalbuminuria was determined in 34% of patients, of which 49% were microalbuminuria positive (fig. 1). The methods used for its determination were: In 65% of patients, MAU was determined by 24-hour urinary albumin excretion (positive for > 30 mg/24 h), in 7% by overnight urinary albumin excretion (positive for > 20 mcg/min), in 17% by albumin/creatinine ratio (positive for > 3 mg/mmol), and in 21% by albumin/creatinine ratio (positive for > 30 mcg/mg).

Table I. Baseline characteristics of the study population

N	1,224
Age (years)	67 ± 10
Female	40%
Hypertensión	100%
Diabetes	34%
Dyslipidemia	59%
Active smoker	14%
Sedentarism	59%
Body mass index (kg/m^2)	29 ± 5
Abdominal circumference (cm)	98 ± 15
Systolic blood pressure (mmHg)	145 ± 18
Diastolic blodd pressure (mmHg)	83 ± 12
Total cholesterol (mg/dl)	200 ± 43
LDL-cholesterol (mg/dl)	121 ± 35
HDL-cholesterol (mg/dl)	48 ± 13
Triglycerides (mg/dl)	151 ± 96
C-reactive protein	11 ± 35
Atrial fibrillation	26%
Left ventricular hypertrophy	22%
Ischemic heart disease	41%
Heart failure	19%
Cerebrovascular disease	8%
Peripheral artery disease	13%
Family history of cardiovascular disease	22%

Determination of glomerular filtration rate

Glomerular filtration rate was calculated by the physician in 11% of patients. A posteriori calculation of GRF by the MDRD equation yielded the following results: Thirty percent of patients had moderate or severe renal dysfunction (GFR < 60 ml/min) and only 21% had normal renal function (GFR > 90 ml/min) (fig. 2). The Cockcroft-Gault formula was used in 57% of patients, the MDRD equation in 31%, and other methods in 11%.

Factors related to determination of microalbuminuria

Urinary albumin excretion was determined in similar proportions in patients with different associated factors. Table II shows the rates of determination and positivity for MAU in different patient subgroups, where it can be seen that MAU rates were higher in diabetics (50% versus 37% nondiabetics, p = 0.009), patients with a history of heart failure (22% *versus* 13% no heart failure, p = 0.021), atrial fibrillation (35% *versus* 20% sinus rhythm, p = 0.001), peripheral artery disease (20% *versus* 11% no peripheral artery disease, p = 0.011) or serum creatinine level > 1.3 mg/dl (19% *versus* 5% creatinine ≤ 1.3 mg/dl, p < 0.001). However, only diabetics and those with electrocardiographic signs of left ventricular hypertrophy had this test performed more often.

Factors related to determination of glomerular filtration rate.

Table III shows the difference in the rates of determination and impairment of glomerular filtration rate between subgroups. GFR was assessed more frequently in patients with serum creatinine > 1.3 mg/dl and those with history of heart failure. Male sex, age and the presence of left ventricular hypertrophy were associated with a reduction in glomerular filtration rate (GFR < 60 mil/min).

Table II. Analysis factors related to determination and positivity of microalbuminuria

		Determination of MAU	p	MAU +	p
Total		34%		49%	
Female	YES	38%	0.42	39%	0.76
	NO	41%		38%	
Age > 65 years	YES	33%	0.29	53%	0.075
	NO	36%		44%	
Diabetes	YES	44%	0.001	50%	0.009
	NO	29%		37%	
Obesity	YES	40%	0.098	41%	0.76
	NO	36%		40%	
Smoking	YES	17%	0.70	20%	0.26
	NO	16%		15%	
Lef ventricular hypertrophy	YES	31%	0.001	36%	0.16
	NO	20%		27%	
History of heart failure	YES	17%	0.25	22%	0.021
	NO	20%		13%	
History of atrial fibrillation	YES	27%	0.48	35%	0.001
	NO	25%		20%	
History of ischemic heart disease	YES	41%	0.72	43%	0.26
	NO	42%		38%	
History of cerebrovascular disease	YES	9%	0.13	9%	0.95
	NO	7%		9%	
History of peripheral artery disease	YES	15%	0.11	20%	0.011
	NO	12%		11%	
Serum creatinine > 1.3 mg/dl	YES	12%	0.45	19%	< 0.001
	NO	14%		5%	

Abbreviation: MAU: increased urinary albumin excretion.

Multivariate analysis

A multivariate analysis was performed to determine the variables that were independently associated with the determination of MAU and/or GFR by the physician. In the analysis adjusted by history of heart failure, atrial fibrillation and serum creatinine > 1.3 mg/dl, age (OR 0.98, 95% CI (0.965-0.999) per year), diabetes (OR 1.86, 95% CI (1.29-2.67)) and left ventricular hypertrophy (OR 1.70, 95% CI (1.13-2.56)) maintained their association and no variable was added.

A similar analysis performed to determine the variables related to positivity of MAU or reduction of GFR < 60 mil/min found that the independently associated variables were female sex (OR 3.42, 95% CI (2.38-4.92)), history of diabetes (OR 1.56, 95% CI (1.08-2.27)), atrial fibrillation (OR 1.99, 95% CI (1.29-3.03)), and electrocardiographic criteria for left ventricular hypertrophy (OR 1.95, 95% CI (1.28-2.97)).

Table III. Analysis of factors related to determination of GFR and values < 60 ml/min

		GFR calculation TFG	p	GFR < 60	p
Total		11%		30%	
Female	YES	12%	0.97	33%	0.030
	NO	12%		42%	
Age > 65 years	YES	11%	0.21	48%	0.009
	NO	13%		26%	
Diabetes	YES	14%	0.11	35%	0.50
	NO	11%		40%	
Obesity	YES	11%	0.72	40%	0.78
	NO	11%		38%	
Smoking	YES	11%	0.69	52%	0.12
	NO	12%		35%	
Left ventricular hypertrophy	YES	10%	0.84	70%	0.001
	NO	11%		25%	
History of heart failure	YES	19%	< 0.001	47%	0.21
	NO	10%		35%	
History of atrial fibrillation	YES	13%	0.30	44%	0.43
	NO	11%		37%	
History of ischemic hearth disease	YES	12%	0.67	36%	0.48
	NO	11%		42%	
History of cerebrovascular disease	YES	12%	0.92	40%	0.91
	NO	12%		38%	
History of peripheral artery disease	YES	10%	0.62	44%	0.62
	NO	12%		37%	
Serum creatinine > 1.3 mg/dl	YES	18%	0.010	82%	< 0.001
	NO	11%		28%	

Abbreviation: GFR: glomerular filtration rate.

Comparison of Cockcroft-Gault and MDRD formulas

Determination of glomerular filtration rates by the Cockcroft-Gault and MDRD formulas showed a correlation of 0.84 ($p < 0.001$). Analysis of the Bland-Altman plot (fig. 3) showed that the mean error between measurement of both formulas was 2.25 ± 38 ml/min, and that the dispersion of this error increased for higher values.

DISCUSSION

Previous studies have shown the importance of assessment of renal function in hypertensive patients. In our analysis of routine practice in cardiology outpatient clinics we observed: 1) Despite the fact determination of MAU is recommended in clinical practice guidelines, it is not part of the work routine of cardiologists in our setting, 2) GFR is seldom calculated, either by direct or indirect estimates, in hypertensive patients by cardiologists, 3) The presence of diabetes as well as other risk factors did not lead cardiologists to actively investigate renal function. Determination of MAU or GFR depended more on the physician than on the patient and his or her clinical context. To our knowledge, this is first study to describe the situation regarding assessment of renal function in real-life cardiology care in Spain, and we think that our results suggest the need to implement strategies designed to achieve more adequate assessment of cardiovascular and renal risk in the clinical practice of Spanish cardiologists.

Microalbuminuria

Over the last years, MAU has become a marker of cardiovascular and renal risk, first used in diabetic patients and later ex-

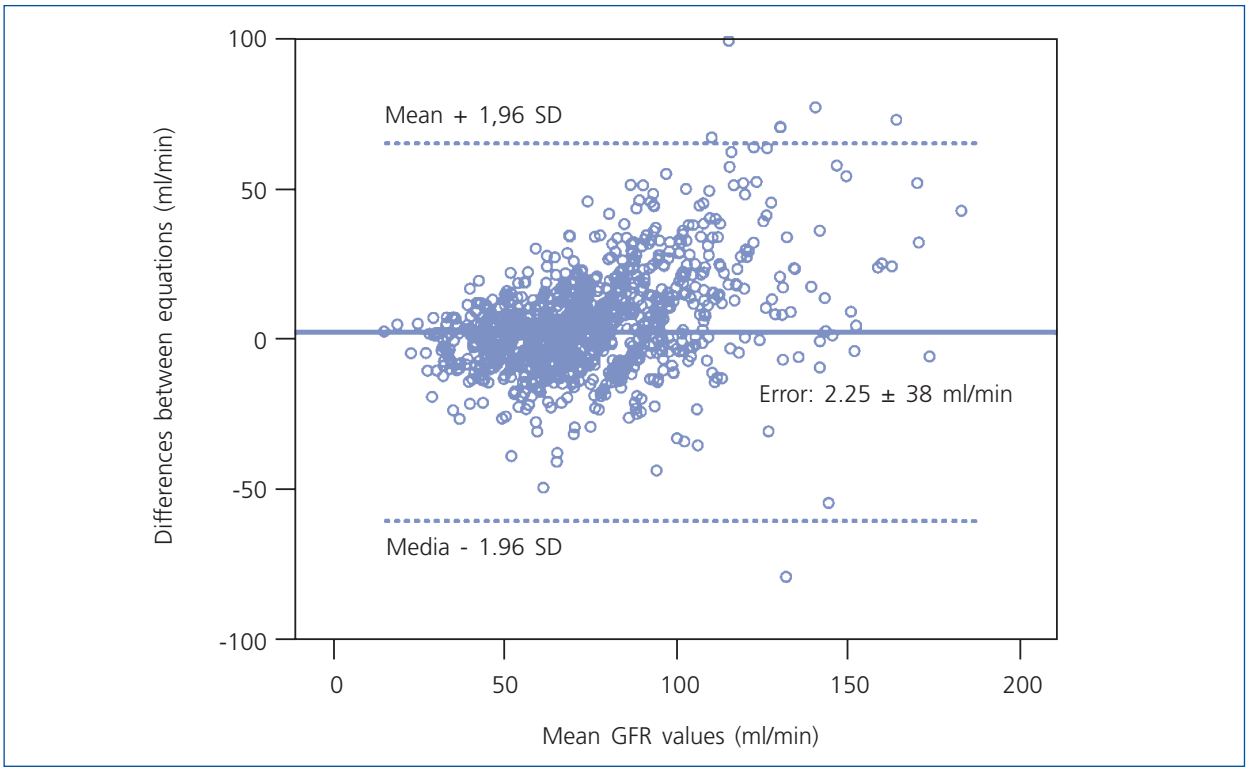

Figure 1.

tended to nondiabetic patients. MAU is associated with a high incidence of death and cardiovascular disease,[3,4] and the fact that a reduction in urinary albumin excretion is associated with a reduction in cardiovascular events makes MAU an ideal marker of risk, not only in risk stratification prior to the start of treatment, but also for monitoring and follow-up of the hypertensive patient under treatment.[13,14] However, the use of this marker in clinical practice is limited; in our registry, urinary albumin excretion was only measured in 34% of patients. Half of these patients showed increased albumin excretion in the range of MAU. We believe that this high rate compared to the 10% and 40%[15,16] reported in previously published studies is due to the high proportion of patients with risk factors or cardiovascular disease. In our sample, diabetes was present in up to 34% diabetes, left ventricular hypertrophy in 22%, ischemic heart disease in 41% and heart failure in 19%. In fact, studies on the prevalence of MAU in patients with cardiovascular disease have reported rates of up to 46.7%.[17]

In the subgroup analysis, we found that although diabetic patients were the ones in whom urinary albumin excretion was tested most often, this measure was taken in less than half of diabetics. The same occurred in patients with left ventricular hypertrophy, even though when MAU is measured in patients with this condition it has a prevalence of up to 62%. Other highly relevant conditions such as a history of atrial fibrillation, heart failure or elevated serum creatinine levels were also not regarded by cardiologists as a reason to make this determination more often. The high rates of positivity for MAU in these conditions reflect the importance of its routine use in clinical practice, a situation that does not appear to be implemented at present.

Glomerular filtration rate

GFR is the best method for assessing overall renal function. Normal GRF varies according to multiple factors, mainly age, sex and weight. Normal GRF in young individuals is approximately 120-130 ml/min/1.73 m^2, and declines physiologically with age. Values lower than 60 ml/min/1.73 m^2 are associated with high rates of complications associated with chronic renal disease.[12]

The high rate of renal failure found in this population of hypertensive patients confirms previous data published with similar populations in our setting.[18,19] These data highlight the importance of calculating GFR, because it identifies a higher number of patients with impaired renal function than a spot measurement of serum creatinine.

The subgroup analysis also revealed that in subgroups at such high risk of renal dysfunction as the elderly, diabetics, or those with a history of heart failure, ischemic heart disease or elevated creatinine, this determination was not performed more often, or if it was, never in more than 20% of patients.

We performed a joint analysis adjusted for the most relevant clinical variables and those that had statistical significance in the univariate analysis to clarify in which subgroups active detection of renal dysfunction was performed in its incipient stages. This analysis showed that renal function was assessed more poorly in older patients despite their having higher rates of MAU and reduction of GFR, whereas patients with diabetes mellitus or electrocardiographic criteria of left ventricular hypertrophy did have better assessment of renal function. In our study, the physicians who requested these determinations did so in nearly all their patients. However, most did not request them regardless of the clinical condition and comorbidity of the patient.

As expected, the correlation between the Cockcroft-Gault and MDRD formulas for GFR calculation was high. The Bland-Altman or difference plot showed that the error between the two formulas was low and that dispersion of this error was greater for higher GFR values, indicating that there are no clinically significant difference between the use of either equation. The simplified MDRD formula has the advantage of not requiring weight, which facilitates its use both in clinical practice and in research. To increase the proportion of patients in whom information on GFR is available, inclusion of determination of GFR by the MDRD formula in the results of routine laboratory tests should be promoted. As mentioned earlier, information on GFR is not only a key element for risk stratification of these patients, but also of great assistance for their follow-up and therapeutic approach.

CONCLUSIONS

The methods currently recommended for early detection of renal dysfunction are underutilized by cardiologists. In view of the proven prognostic value of MAU and GFR, the low cost of testing and the existence of specific treatments for both conditions, we should make a collective effort to promote their determination in clinical practice.

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