Importance of Recognizing Occult Renal Disease in Hypertensive Patients

Lorenzo Fácila,[a] Vicente Bertomeu-González,[b] Vicente Bertomeu,[b] José R. González-Juanatey,[c] Pilar Mazón,[c] and Pedro Morillas[b], on behalf of the researchers of the RICAR group

[a]Servicio de Cardiología, Hospital Provincial de Castellón, Castellón, Spain
[b]Servicio de Cardiología, Hospital de San Juan de Alicante, San Juan de Alicante, Alicante, Spain
[c]Servicio de Cardiología, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, A Coruña, Spain

Introduction and objectives. Occult renal disease (ORD) is a condition that characterizes the early stages of renal failure and which cannot be detected by routine monitoring. The aims of this study were to determine the prevalence of ORD in hypertensive patients attending cardiology outpatient clinics and to identify its relationship with specific cardiovascular risk factors or treatment.

Methods. A cross-sectional, retrospective, multicenter observational study was carried out in 1214 hypertensive patients attending cardiology outpatient clinics.

Results. Data from 1190 patients (98%) were analyzed. In 11%, the glomerular filtration rate (GFR) was calculated by the attending cardiologist using the Modification of Diet in Renal Disease equation. Overall, 9.5% of patients were found to have ORD. Affected patients were more likely to be female, to be older, to have a history of dyslipidemia, diabetes, a sedentary lifestyle or atrial fibrillation, or a long history of hypertension compared with those without ORD, but were less likely to have a history of dyslipidemia, diabetes, or a sedentary lifestyle than those with renal failure. There was no significant difference in treatment. Moreover, ORD was observed in 2.9% (2 of 68) of those aged under 50 years, in 3.3% (7 of 210) aged 50-60 years, in 9.3% (37 out of 398) aged 60-70 years, and in 13.5% (70 out of 518) aged over 70 years.

Conclusions. Almost 10% of hypertensive patients reviewed by a cardiologist had moderate renal dysfunction that had not been investigated. They represent an unrecognized population with an intermediate cardiovascular risk. Consequently, it is recommended that the GFR should be calculated, especially in women and older patients.

Key words: *Arterial hypertension. Renal dysfunction. Cardiovascular disease.*

Importancia de la detección de la enfermedad renal oculta en pacientes hipertensos

Introducción y objetivos. La enfermedad renal oculta (ERO) es una entidad que define los estadios más iniciales de insuficiencia renal y no se detecta con los métodos usados habitualmente. El objetivo es determinar la prevalencia de ERO en los pacientes hipertensos en consultas de cardiología y su relación con los distintos factores de riesgo y tratamientos cardiovasculares.

Métodos. Estudio observacional, transversal, retrospectivo y multicéntrico que se llevó a cabo en 1.214 hipertensos de consultas de cardiología.

Resultados. Se analizó a 1.190 pacientes (98%). El filtrado glomerular (FG) fue calculado (MDRD) por el cardiólogo responsable en el 11% de los pacientes. Tras su determinación a posteriori, el 9,5% presentaba ERO, más probablemente mujeres, con más edad, más antecedentes de dislipemia, diabetes, sedentarismo y fibrilación auricular y más años de evolución de la hipertensión que los pacientes sin disfunción, y menos antecedentes de dislipemia, diabetes y sedentarismo que aquellos con disfunción. En cuanto al manejo terapéutico, fueron escasas las diferencias. La detección de ERO por debajo de 50 años fue del 2,9% (2 de 68); entre 50 y 60 años, el 3,3% (7 de 210); entre 60 y 70, el 9,3% (37 de 398), y por encima de 70 años, el 13,5% (70 de 518).

Conclusiones. Casi un 10% de los pacientes hipertensos controlados por cardiólogos están infradiagnosticados en cuanto a disfunción renal moderada se refiere, con lo que no se detecta a una población con riesgo cardiovascular intermedio. Por ello es recomendable la utilización de fórmulas para determinar el FG, sobre todo en mujeres y pacientes mayores.

Palabras clave: *Hipertensión arterial. Disfunción renal. Enfermedad cardiovascular.*

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Correspondence: Dr L. Fácila Rubio.
Servicio de Cardiología. Hospital Provincial de Castellón.
Avda. Dr. Clara, 19. 12002 Castellón de la Plana. España.
E-mail: lfacila@gmail.com

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ABBREVIATIONS

GFR: glomerular filtration rate
KF: kidney failure
ORD: occult renal disease

INTRODUCTION

Chronic kidney failure (KF) is defined as a reduction in renal function manifested as a glomerular filtration rate (GFR) or estimated creatinine clearance of <60 mL/min/1.73 m^2 or as the presence of kidney damage maintained for at least 3 months.[1] This definition allows the different stages of KF to be stratified according to the GFR. The standard method used is the measurement of creatinine clearance in 24 h urine, but this can sometimes return very erroneous results, usually a consequence of errors in urine collection. Therefore, in everyday practice, the assessment of kidney function is usually determined from the serum creatinine concentration, even though it is known that many factors (especially age, sex, and muscular mass) can influence it.[2,3] The results can therefore only be regarded as a crude approximation of true kidney function. It is not uncommon to eventually detect reduced kidney function in subjects with lower levels of muscular mass, with lower body weights or who are older, even though they appear to have normal serum creatinine concentrations.

In recent years, however, new methods have been validated based on predictive equations that take into account the serum creatinine concentration plus the sex, age, and body weight of the patient.[4,5] Several studies (including a recently published European study)[6] with large numbers of patients have shown these equations to be the most reliable for estimating the GFR, and report that they even allow kidney dysfunction to be estimated at early stages when serum creatinine levels are normal.

Occult renal disease (ORD), which cannot be detected by normal methods involving the determination of serum creatinine, is the term given to the earliest stages of KF. Patients with ORD have creatinine levels within the normal range but show an abnormal GFR. They are therefore probably at a greater risk of cardiovascular disease. The aim of the present work was to determine the prevalence of ORD in patients with high blood pressure attending cardiology consultations, and to investigate its relationship with the classic cardiological risk factors and the treatment being received.

METHODS

Study Design

The study subjects of this cross-sectional, observational, retrospective, multi-center study, which involved no pharmacological intervention, were 1214 consecutive patients with high blood pressure recruited during cardiology consultations. A total of 124 randomly chosen centers (hospital and out-patient) across all of Spain's regions took part. After receiving training, each cardiologist researcher included his/her last 10 patients with a diagnosis of high blood pressure, all of whom met all inclusion criteria and failed to meet any exclusion criterion. The inclusion criteria were age >18 years and a confirmed diagnosis of high blood pressure according to current clinical practice guidleines.[7] The exclusion criteria were: kidney disease with serum creatinine >2 mg/dL, current hospitalization, and those with a life expectancy of <3 months. The study was approved by the independent ethics committee of the participating reference hospital.

Data Collection

The following data were collected using a questionnaire: age, sex, waist measurement, body weight, height, the presence of diabetes mellitus or dyslipidemia, whether the patient was an active smoker (defined as having smoked at least 1 cigarette in the previous year), the presence of obesity (body mass index [BMI] ≥30), whether the patient led a sedentary lifestyle (not walking or performing at least 30 min exercise at least 3 days per week), and the presence of cardiovascular disease or a family history of such disease.

The presence of left ventricular hypertrophy was defined according to the electrocardiographic criteria of Sokolow-Lyon (sum of the R wave for V_{5-6} + the S wave for V_1 >35 mm). Biochemical data were obtained from the last test results obtained within the 6 months prior to inclusion. The GFR was calculated by the cardiologist researchers in only 11% of cases. Kidney dysfunction was deemed present when patients showed a serum creatinine concentration of ≥1.3 mg/dL or a GFR of <60 mL/min/1.73 m^2. In the remaining cases the GFR was determined a posteriori by the data-handling researchers using the Modification of Diet in Renal Disease (MDRD) formula. Occult renal disease was deemed present in patients with no diagnosis of kidney dysfunction from their cardiologist researcher, but who showed a GFR of <60 mL/min/1.73 m^2. A GFR of ≥60 mL/min/1.73 m^2 was regarded to reflect normal kidney function.

Statistical Analysis

Continuous variables were expressed as means (standard deviation), and were compared using either ANOVA for non-paired data or the Welch test if the homoscedasticities of the variances were significantly different. The normality of the distribution was tested using stem and leaf plots. Categorical variables were expressed as percentages of the study population and compared using the χ^2 test. All null hypotheses were rejected if there was a type I error or an alpha error of <.05. All calculations were performed using SPSS v.15 software.

RESULTS

Of the 1214 original patients, data were collected for 1190 (98%); the remainder were excluded. The mean age of the patients analyzed was 67 (10) years; 40% were women. Some 34% were diabetic and 59% suffered dyslipidemia. Some 15.7% had a background of smoking, 56.1% had a sedentary lifestyle, 65% of the men and 21% of the women showed abdominal obesity, and 20.8% had established cardiovascular disease (heart failure in 18.5%, atrial fibrillation in 25.3%, evidence of left ventricular hypertrophy in the ECGs of 32.6%, ischemic heart disease in 44.5%, cerebrovascular accident in 6.8%, and peripheral artery disease in 12.6%). Some 19.7% of the patients with high blood pressure were treated with 1 drug, 33.4% with 2, 29.2% with 3, and 17.7% with more than 3.

Determination of the GFR

The GFR of 11% of the patients was calculated by the attending cardiologist researcher (55.7% via the Cockroft-Gault formula, 32.8% via the MDRD equation, and 11.5% via another method). Among the patients for whom the GFR was determined *a posteri* by the MDRD equation (performed by the data-handling researchers), 70.5% were found to have normal kidney function, 9.5% had ORD, and 20% had recognized KF (Figure 1).

As shown in Table 1, the patients with ORD were more likely to be women, older, to have a background of dyslipidemia or diabetes, to have a sedentary lifestyle or suffer atrial fibrillation, and to have suffered high blood pressure for longer compared to those with normal kidney function. In addition, they were less likely to have a background of dyslipidemia, diabetes or to have a sedentary lifestyle than patients with kidney dysfunction.

Few differences were seen with respect to the degree of KF in terms of therapeutic management with thiazides, calcium channel antagonists, angiotensin antagonists, alpha blockers, or angiotensin converting enzyme inhibitors. However, as KF became worse, the use of loop diuretics, anti-aldosterone agents, and beta-blockers increased (Table 2).

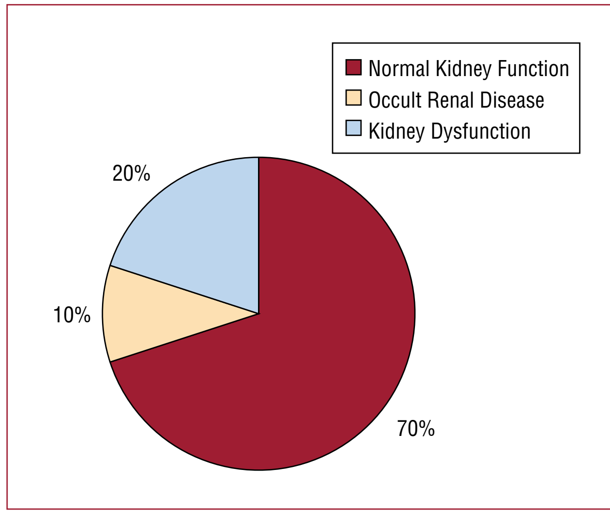

Figure 1. Distribution of the population with respect to kidney function.

Figure 2 shows that, with increasing age, the MDRD equation detected more cases of ORD. Among patients under 50 years of age, 2.9% (2 out of 68) had ORD; between 50 and 60 years the figure rose to 3.3% (7 out of 210), between 60 and 70 years it reached 9.3% (37 out of 398), and above 70 years it reached 13.5% (70 out of 518).

DISCUSSION

The results of the present study show that approximately 10% of the patients with high blood pressure being followed by a cardiologist were underdiagnosed with respect to moderate KF (GFR <60 mL/min/1.73 m^2). The detection of kidney dysfunction from the very early stages (even when creatinine levels are normal) is very important, since it requires adjustment of the doses of different agents (eg, digoxin, beta-blockers, and anticoagulants, etc) as well as monitoring for the appearance of their toxic effects. It is also a cardiovascular mortality/morbidity risk factor in its own right for the general population, for those with cardiovascular risk factors (high blood pressure, diabetes), and those with established cardiovascular disease.[7,8] A clear inverse relationship has been seen between initial kidney function and the later risk of cardiovascular death and complications.[9,10]

In a study involving primary care patients, Otero et al,[11] using the MDRD equation, detected a prevalence for ORD of 13% in a population of 1059 subjects over 18 years of age. Duncan et al[12] detected

TABLE 1. **Epidemiological Differences Between Subgroups of Patients According to Kidney Function**

	NKF (n=839)	ORD (n=113)	KD (n=238)	*P* for Trend
Age, mean (SD), y	65.3 (10.4)[a]	70.9 (8.3)	71.1 (8.9)	<.001
Men n (%)	556 (67)[a]	3 (2.6)	151 (63.7)[a]	<.001
Body weight, kg	79.9 (14.7)[a]	74.7 (12.3)	77.7 (11.9)	.001
Height, cm	165.6 (9.3)[a]	159.8 (7.2)	164.8 (9.2)	.05
BMI	29.1 (5.1)	29.2 (4.4)	28.7 (4.1)	NS
Waist measurement, cm	99.4 (13.8)	96.4 (14.4)	97.3 (16.7)	NS
Years of HBP	8.2 (6.6)[a]	8.9 (5.8)	9.9 (7.2)	.021
Dyslipidemia, %	47.9	48.3	56.7[a]	.014
Diabetes mellitus, %	29a	37.1	42	<.001
Smokers, %	17.1	4.3	17.6	NS
Sedentary lifestyle, %	53.1[a]	62.1	66.9	.001
Family background, %	20.6	17.2	25.3	NS
Background of IHD, %	38.2	25.1	44.5	NS
Angina, %	27.8	21.6	36.3	NS
AMI, %	22.4	11.2	27.3	NS
Revascularization, %	22	12.9	23.7	NS
AF, %	21.6[a]	33.6	34.7	0.01
Ictus, %	6.1	7.8	9	NS
Peripheral artery disease, %	11.4	10.3	18[a]	.025
Mean SBP, mm Hg	145.2 (18.3)	145 (17.6)	142.3 (17.9)	NS
Mean DBP, mm Hg	83.9 (11.4)	83.4 (11.7)	83 (11.9)	NS
MDRD, mL/min/1.73 m^2	83.43 (19.5)	52.3 (4.6)	47.1 (11.8)	<.001
Creatinine, mg/dL	1.1 (0.86)[a]	1.29 (0.92)	1.51 (0.33)[a]	<.001
LVH, mm	25.5 (9.9)	27.5 (9.3)	28.7 (11.4)	.005

AF indicates atrial fibrillation; AMI, acute myocardial infarction; BMI, body mass index; DBP, diastolic blood pressure; HBP, high blood pressure; IHD, ischemic heart disease; KD, kidney dysfunction; LVH, left ventricular hypertrophy (according to the electrocardiographic criteria of Sokolow-Lyon [sum of the R wave for $V_{5\text{-}6}$ + the S wave for V_1 >35 mm); NKF, normal kidney function; ORD, occult renal disease; SBP, systolic blood pressure.

[a]For some variables no differences were seen between the 3 groups of patients, even though the *P* for trend was <.05. A superíndex denotes a significant difference between the marked group and the ORD group.

TABLE 2. **Differences in Treatment Received by the Different Patient Groups According to Kidney Function**

	NKF (n=839)	ORD (n=113)	KD (n=238)	*P* for Trend
No treatment, %	1.9	0	1.2	NS
Thiazides, %	24.2	34.5	28.2	NS
Spironolactone, %	6.8	7.8	13.9	.001
Loop diuretics, %	15.9	28.4	35.5	<.001
Calcium channel antagonists, %	29.2	32.8	27.3	NS
Beta-blockers, %	46.8	47.4	58	.003
ARA-II, %	41.5	50.9	46.1	NS
Alpha-blockers, %	5.8	4.3	4.1	NS
ACEi, %	38.2	34.5	38.8	NS

ACEi indicates angiotensin converting enzyme inhibitors; AF, atrial fibrillation; ARA-II, angiotensin II receptor antagonists; KD, kidney dysfunction; NKF, normal kidney function; ORD, occult renal disease.

ORD in 15.2% of 2781 Canadian outpatients using the Cockcroft-Gault method, and reported a GFR threshold of 50 mL/min. In the present study the ORD figures were smaller since the patients examined were those in whom the cardiologist researcher made no attempt to detect KF–but who showed moderate kidney dysfunction in later analysis performed by the data-handlers (GFR <60 mL/min/1.73 m^2), ie, patients in whom this condition was clearly undetected by the cardiologist. In these other studies, the number of patients in whom a change in kidney function was detected by the attending physician was not taken into account.

Detecting patients with ORD is very important in routine practice since they have more cardiovascular risk factors than those with normal kidney function, but fewer than those with known kidney dysfunction (Table 1). It is for this reason that the guidelines of the Sociedad Española de Nefrología y Cardiología (the Spanish Nephrology and Cardiology Society) recommend that the GFR be systematically determined using formulae that contemplate the

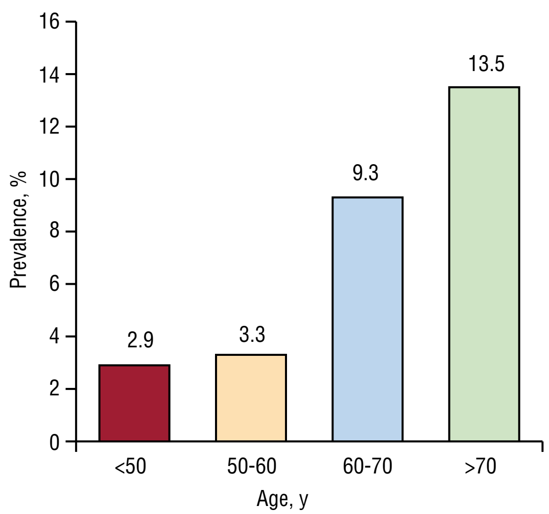

Figure 2. Prevalence of occult renal disease according to age.

creatinine concentration as well as other variables (mainly sex and age), and, if possible, that GFR results be provided alongside those for serum creatinine.[13] This would help in the detection of patients with intermediate cardiovascular risk. Furthermore, since moderate and severe kidney dysfunction (GFR <60 mL/min/1.73 m^2) are, in their own right, independent cardiovascular risk factors,[14] such information would help in establishing correct treatment, help prevent the dysfunction from becoming any worse, and help to better stratify patients. In the present work, the patients with ORD were treated pharmacologically in a manner similar (although not with diuretics or spironolactone) to those who did not show this abnormality; probably because the attending cardiologist was unaware of the problem. With respect to the use of anti-aldosterone agents, an increase was seen as KF became worse–yet these agents can actually worsen kidney function and have very serious side effects. The GFR should, therefore, always be determined before anti-aldosterone therapy is embarked upon.

The use of the MDRD formula was very helpful in women and older patients (Figure 2). This was mainly because they have a smaller muscular mass; therefore, although their creatinine levels might appear normal, they might be hiding a true case of KF.[12,15]

The limitations of this study are those inherent to any cross-sectional, observational study: no randomized stratification of the patients was possible and no conclusions to be drawn regarding risk factors. In addition, the data recorded, which influenced the presence of ORD, were limited in their scope (eg, neither the patients' hypertension grade, nor the level of the cardiovascular repercussions of their high blood pressure, nor the relationship between their high blood pressure and the treatment received could be established). Finally, the biochemical test data, which were taken from tests performed in the 6 months prior to the study, may no longer have been fully reliable.

CONCLUSIONS

Approximately 10% of the patients with high blood pressure attended to by the cardiologist researchers in this study were underdiagnosed with respect to moderate kidney dysfunction (or ORD). Thus, a subpopulation with an increased number of cardiovascular risk factors went undetected–a subpopulation whose pharmacological management was inadequate. It is highly recommended that kidney dysfunction be detected early via the use of formulae for determining the GFR based on serum creatinine levels, age and sex. This would be especially useful in women and in patients of advanced age.

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