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## ORIGINALES

# *Renal failure prevalence among Spanish Primary Care Centers: the EROCAP study*

**Á. L. M. de Francisco*, J. J. De la Cruz**, A. Cases***, M. de la Figuera****, M. I. Egocheaga*****, J. I. Górriz******, J. I. Llisterri*******, R. Marín******** and A. Martínez Castelao*********

*Nephrology Department. Marqués de Valdecilla University Hospital. Santander. **Department of Preventive Medicine and Public Health. School of Medicine. Autonomous University of Madrid. ***Nephrology Department. Clínic Hospital. Barcelona. ****La Mina Primary Care Center. Barcelona. *****Isla de Oza Primary Care Center. Madrid. ******Nephrology Department. Peset Hospital. Valencia. *******Joaquín Benlloch Primary Care Center. Valencia. ********Nephrology Department. Hospital Universitario Central de Asturias. Oviedo. *********Nephrology Department. Bellvitge University Hospital. Barcelona.

**SUMMARY**

*This cross-sectional, multicenter study investigated the prevalence of chronic kidney disease and associated disorders, in an adult population sample (> 18 years old) attending Primary Care services in Spain. Estimated glomerular filtration rate (Modification Diet in Renal Disease equation) was used for analysis of kidney disease prevalence according to NFK-KDOQI (The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) stages. Data were collected on serum creatinine, other laboratory parameters blood pressure, and medical history of cardiovascular risk factors or disease (hypertension, dislypidemia, diabetes, congestive heart failure, coronary artery disesase, stroke or peripheral arteriopathy) in 7,202 patients attending Primary Care Centers. 47.3% were males, mean age 60,6 ± 14,3 years, BMI 28.2 ± 5.3, with 27,6% overweight (27-30 kg/m$^2$) and 32,1% obese (BMI ≥ 30 kg/m$^2$), The prevalence of cardiovascular risks factors were: absence in 17.3%, one factor 26.9% two 31.2%, and 23.6% presented three or more The frequency of CV risk factors was: hypertension (66.7%), dyslipidemia (48%) and diabetes (31.5%). Congestive heart failure, coronary artery disease, stroke or peripheral vascular disease frequency was lower than 10% The prevalence of eGFR < 60 ml/min × 1.73 m$^2$ was: stage 3 (30-59 ml/min/1.73 m$^2$) 19.7%; stage 4 (15-29 ml/min/1.73 m$^2$) 1.2%; stage 5 no dialysis (GFR < 15 ml/min) 0.4%. This prevalence increased with age in both sexes and 33,7% of patients attending Primary Care services over 70 years presented a eGFR < 60 ml/min. Of the total patients with eGFR < 60 ml/min 37.3% had normal serum creatinine levels. This study documents the substantial prevalence of significantly abnormal renal function among patients at Primary Care level. Early identification and appropriate nephrological management of these patients with renal disease is an important opportunity for an adequate prescription of drugs that interfere with renal function, to delay the progression of renal disease and modify CV risk factors.*

Key words: ***Epidemiology. Chronic kidney disease. Primary care. Cardiovascular risk factors.***

**Correspondence:** Dr. Ángel Luis Martín de Francisco
E-mail: martinal@unican.es

## PREVALENCIA DE INSUFICIENCIA RENAL EN CENTROS DE ATENCIÓN PRIMARIA EN ESPAÑA: ESTUDIO EROCAP


### RESUMEN

*La prevalencia de la insuficiencia renal en pacientes que acuden a los Centros de Atención Primaria (CAPs) es desconocida en España. Presentamos un estudio epidemiológico transversal y multicéntrico en una población adulta (mayor de 18 años) que acude a los CAPs en España. Para clasificar a los pacientes según los estadios NFK-KDOQI (The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative) se estimó el filtrado glomerular mediante la ecuación de MDRD. Se recogieron los datos de creatinina sérica, otros índices de laboratorio, presión arterial e historia médica de factores de riesgo cardiovascular (HTA, dislipemia, diabetes, insuficiencia cardíaca congestiva, enfermedad coronaria, ACVA o arteriopatía periférica) en 7.202 pacientes. El 47,3% fueron varones, edad media de 60,6 ± 14,3 años; IMC 28,2 ± 5,3; con un 27,6% de sobrepeso (27-30 kg/m$^2$) y un 32,1% de obesidad (IMC mayor o igual a 30 kg/m$^2$). La prevalencia de factores de riesgo cardiovascular fue: ausencia en el 17,3%, un factor en el 26,9%, dos en 31,2% y tres o más en el 23,6%. La frecuencia se distribuyó en: hipertensión en el 66,7%, dislipemia 48%, diabetes 31,5%. La presencia de trastornos clínicos asociados (Insuficiencia cardíaca congestiva, enfermedad coronaria, ACVA o arteriopatía periférica) fue inferior al 10%. La prevalencia de un filtrado glomerular estimado (eFG) inferior a 60 ml/min/1,73 m$^2$ fue: estadio 3 (FGe 30-59 ml/min/1,73 m$^2$) 19,7%; estadio 4 (15-29 ml/min/1,73 m$^2$) 1,2%; estadio 5 no en diálisis (eFG < 15 ml/min) 0,4%. Esta prevalencia aumentó con la edad en ambos sexos y el 33,7% de los pacientes que acudieron a los CAPs mayores de 70 años presentaron un eFG < 60 ml/min/1,73 m$^2$. Del total de pacientes con eFG inferior a 60 ml/min 37,3% tuvieron unos niveles normales de creatinina sérica. Este estudio documenta la prevalencia importante de alteraciones significativas de la función renal en pacientes que acuden a las consultas de atención primaria. Es importante una identificación temprana y un cuidado nefrológico apropiado en estos pacientes con la finalidad de evitar la prescripción de drogas que interfieren con la función renal, retrasar la progresión de la enfermedad renal y especialmente modificar los factores de riesgo cardiovasculares asociados.*


Palabras clave: ***Epidemiología. Enfermedad renal crónica. Atención primaria. Factores de riesgo cardiovascular.***

### INTRODUCTION AND OBJECTIVES

Chronic renal disease represents one of the major mortality causes in industrialized countries. And this is not lonely due to those patients reaching the stage of needing dialysis or transplantation therapy, which progression is, many times, worse than those with advanced cancer, but also to those not reaching dialysis but with proteinuria of decreased glomerular filtration rate in which there is an association with a high prevalence of cardiovascular complications.[1-2]

In the year 2005, more than 40,000 people in Spain, that is to say, around 1,000 per million population were on renal replacement therapy, a figure that will probably increase within the next 10 years due to progressive aging of the population and the increase in the prevalence of other chronic conditions such as diabetes mellitus, hypertension and obesity. It is very similar to what happens in other developed countries, in which although the incidence tends to stabilize the prevalence of patients receiving renal function replacement therapy, either by dialysis or renal transplantation, is still considerably increasing reaching figures up to 1,500-1,800 per million population in the year 2003 in Japan, Taiwan and the USA.[3-4] And this data are considerably lower than those considered for developing countries.

In most of the countries, this increase is essentially based on aged population, being higher than 50% in patients older than 65 years, with the subsequent morbimortality with transcendent socio-sanitary consequences.[6] This distribution is similar in Spain, with most of the population on renal replacement therapy aged more than 65 years.[3]

This clear increase in the prevalence of end-stage chronic renal disease (CRD) has led to heightened interest in CRD-related epidemiological studies. One of the major problems with these studies has been the use of a correct methodology to assess renal function. Previous studies based on plasma creatinine were not appropriate since this parameter depends on age and muscle mass. Recently, the recently published K-DOQI guidelines on the diagnosis and classification of CRD from the National Kidney Foundation[6] defined CRD as the condition in which there is renal damage (determined by the presence of proteinuria of anatomical abnormalities) and/or there is GFR < 60 ml/1.73 $m^2$ for more than three months. The fact that determining GFR is a costly and complex procedure has led to the use of several methods calculating the estimated GF (eGF) derived from serum creatinine level, which include the Cockcroft-Gault equation and several other equations derived from the population included in the MDRD study;[7] these equations have become popular for both research and the clinical practice and are being introduced little by little in routine analysis in the different countries. The Spanish Society of Nephrology and the Spanish Society of Clinical Chemistry have recently developed a consensus document on this issue.[3]

Taking into account the high prevalence of elderly people with cardiovascular complications such as hypertension and diabetes attending the Primary Care Centers and in whom medications interfering with renal function are prescribed, we have developed this study with a main goal: to know the prevalence of chronic renal failure (defined as glomerular filtration rate < 60 mL/min) in a representative sample of the Spanish population attending the PC centers. The secondary end-point was to know the prevalence of cardiovascular disease and chronic renal disease-associated cardiovascular risk factors.

## PARTICIPANTS AND METHODS

- *Study design:* This is a cross-sectional and multicenter epidemiological study on the population attending primary care centers. A non-probabilistic stratified sampling by Spanish geographical locations is performed by consecutively selecting the two first patients attending the PC center on three consecutive days. In case of not wanting to participate, that patient was replaced by the next consecutive one, and so on, until completing 6 patients per investigator. The study implies one single visit during which clinical and analytical variables of interest were selected. In many cases, recent analytical variables were selected, no older than 3 months if available. The weight, height, and blood pressure were taken on two times.
- *Subjects:* Inclusion criteria: patients of both genders, > 18 years old, having a consultation for any reason at the Primary Care Center, and giving their informed consent to participate into the study. There were no exclusion criteria but refusal to give informed consent.
- *Measurements:* Bio-demographical data, cardiovascular risk pathology, analytical data and pharmacological therapies related with AHT, diabetes and dyslipidemia. Weight and height: taken with semi-undressed and barefoot patient, using calibrated scales. Blood pressure: BP measurement was done as recommended by the Spanish Society of Hypertension-Spanish League against Arterial Hypertension[8] taking after a five-minutes rest two measurements with the patient sitting. In case of finding differences equal or higher than 5 mmHg between both measurements, a third one was taken. A recently calibrated mercury or arenoid sphingomanometer or validated automated electronic devices were used.
- *Medication:* the information on medications refers to the time of the visit.
- *Definitions.*
  - Renal failure: eGF < 60 mL/min/1.73 $m^2$. The K/ DOQI classification was used to define CRD stages (Table I). For this study, CRD at stages III-IV was considered as being clinically significant, which represents an estimated glomerular filtration rate < 60 mL/min/ 1.73 $m^2$.
  - Obesity: BMI > 30 Kg/$m^2$.
  - AHT: verified BP values > 140 and/or 90 mmHg or patient on anti-hypertensive therapy.

**Table I.** K/DOQI Classification of CRD stages

| Stage | Description | GFR (mL/min/1,73 $m^2$) |
|---|---|---|
| 1 | Renal damage with normal or elevated GFR | ≥ 90 |
| 2 | Renal damage with GFR slightly decreased | 60-89 |
| 3 | Moderate decrease in GFR | 30-59 |
| 4 | Severe decrease in GFR | 15-29 |
| 5 | Renal failure | < 15 (or dialysis) |

CRD: Chronic Renal Disease.

– Diabetes: baseline plasma glucose > 7.0 mmol/L (126 mg/dL), postprandial plasma glucose > 11.0 mmol/L (198 mg/dL) or on anti-diabetic therapy.
– Dyslipidemia: total cholesterol > 6.5 mmol/L (250 mg/dL), LDLc > 4.0 mmol/L (155 mg/dL) or HDLc < 1.0 in males, < 1.2 mmol/L in females (< 40 and < 48 mg/dL, respectively).
– Cigarette smoking: a smoker was considered if the patient had smoked at least one cigarette within the last month.
– Anemia: Hb < 12 g/dL.
– Hyperkalemia: K > 5.2 mEq/L. Hypokalemia: K < 3.5 mEq/L.
– Associated cardiovascular pathology:
  1. Cerebrovascular disease: documented history of hospital admission for ischemic CVA: hemorrhagic CVA or TIA.
  2. Ischemic heart disease: documented history of hospital admission or specialized consultation for heart angina, AMI or myocardial reperfusion.
  3. Heart failure: documented history of symptoms and signs with need for hospital admission and confirmation by chest X-ray.
  4. Peripheral arteriopathy: evident symptoms of intermittent claudication. Also, ankle/arm index < 0.9. Documented history with vascular radiology of arterial stenosis. Angioplasty or revascularization surgery. Abdominal aortic aneurysm documented at least by ultrasound.

• Estimated GFR. GFR is calculated from the abbreviated or modified (abbreviated Levey's formula) MDRD as:

$$GFR = 186{,}3 \times (\text{Serum Creatinin})^{-1{,}154} \times \text{Age}^{-0{,}203} \times (0{,}742 \text{ in females})$$

For further comparison analysis with the Cockcroft-Gault formula (Ccr), GFR was also calculated as:

$$Ccr = \frac{(140 - age) \times weight(Kg)}{Crs(mg/dL) \times 72} \; (\times 0{,}85 \text{ in females}) \times \frac{1{,}73}{SC}$$

Being…

$$SC(m^2) = 0{,}20247 \times height(m)^{0{,}725} \times weight(Kg)^{0{,}425}$$

• Statistical analysis. The statistical study comprises three steps:

a) Descriptive study: Quantitative variables show absolute frequencies (n) and percentages for each category, with confidence intervals for the percentage of


*Fig. 1.—Percentages are calculated based on 6,173 (66.9%) patients whose origin is known.*

the main variables. The distribution form of quantitative variables is studied, in all cases coming close to normal distribution, by means of either the Kolmogov-Smirnov goodness of fit or the central limit theorem, so that the mean is calculated as the central tendency measurement of and standard deviation as the dispersion measurement.

b) Univariate analysis. From the classification with the abbreviated MDRD formula, the relationship of socio-demographical variables, the associated cardiovascular risk factors, the lifestyle-dietary habits, as well as obesity, treatments, anemia, and potassium levels and all the remaining analytical data categorized according to levels of Chronic Renal Disease are studied by the Pearson's chi-squared test, the Fisher's test, or the maximal likeliness correction, as determined by the sample size. For ordinal qualitative variables, the chi squared test for tendencies is calculated.

In order to study the relationship between quantitative variables and Chronic Renal Disease, fitness to normal distribution is first calculated by the Kolmogorov-Smirnov goodness of fit test; if these variables are close to a Gaussian distribution for each group of Chronic Renal Disease, the student's test for independent samples is use; in other case, the Mann-Whitney U test is used.

c) Regression analysis. We have chosen GFR as the dependent variable (≥ 60 mL/min vs. < 60 mL/min); as a first step, a simple conditional logistic regression analysis is performed, and then with the independent variables (age, gender, personal history, lifestyle-dietary habits, and analytical data) obtaining a p value < 0.1 by Wald's statistic, a multiple conditional logistic regression analysis is performed (stepwise forward) with likelihood at entry of 0.1 and at the exit of 0.15.

**Table II.** Clinical characteristics of the sample by gender and total

| Variables | Males 3,407 (47.3%) | Females 3,795 (52.7%) | Total 7,202 |
|---|---|---|---|
| Age (years) | 59.8 ± 13.8 | 61.1±15.0 | 60.6 ± 14.3 |
| Age groups n (%) | | | |
| < 40 years | 283 (8.3) | 362 (9.5) | 645 (9.0) |
| 41-60 years | 1,370 (40.2) | 1,274 (33.6) | 2,644 (36.7) |
| 61-70 years | 906 (26.6) | 983 (25.9) | 1,889 (26.2) |
| 71 and more years | 848 (24.9) | 1,176 (31.0) | 2,024 (28.1) |
| Weight (kg) | 81.0 ± 12.6 | 70.6 ± 12.7 | 75.6 ± 13.7 |
| Height (cm) | 169.6 ± 7.5 | 159.0 ± 7.5 | 164.0 ± 9.2 |
| BMI (kg/m$^2$) | 28.2 ± 3.9 | 28.0 ± 5.1 | 28.1 ± 4.6 |
| Diabetes Mellitus Type I | 117 (3.4) | 121 (3.2) | 238 (3.3) |
| Diabetes Mellitus Type II | 1,046 (27.6) | 988 (29.0) | 2,034 (28.2) |
| AHT | 2,320 (68.1) | 2,481 (65.4) | 4,801 (66.7) |
| Dyslipidemia | 1,734 (50.9) | 1,726 (45.9) | 3,460 (48.0) |
| Ischemic heart disease | 441 (12.9) | 254 (6.7) | 695 (9.7) |
| Heart failure | 181 (5.3) | 201 (5.3) | 382 (5.3) |
| Cerebrovascular disease | 140 (4.1) | 118 (3.1) | 258 (3.6) |
| Peripheral arteriopathy | 235 (6.9) | 170 (4.5) | 405 (5.6) |
| Current smokers* | 816 (26.4) | 395 (11.5) | 1,211 (18.6) |
| **Current therapies** | | | |
| ACEI | 958 (28.1) | 942 (24.8) | 1,900 (26.4) |
| ARA II | 1,157 (34.0) | 1,223 (32.2) | 2,380 (33.0) |
| Calcium channel blockers | 453 (13.3) | 443 (11.7) | 896 (12.4) |
| Beta-blockers | 418 (12.3) | 326 (8.6) | 744 (10.3) |
| Diuretics | 1,042 (30.6) | 1,292 (34.0) | 2,334 (32.4) |
| Alpha-blockers | 218 (6.4) | 85 (2.2) | 303 (4.2) |
| Other anti-hypertensive | 57 (1.7) | 49 (1.3) | 106 (1.5) |
| Oral anti-diabetic | 827 (24.3) | 866 (22.8) | 1,693 (23.5) |
| Insulin | 207 (6.1) | 285 (7.5) | 492 (6.8) |
| ASA | 680 (20.0) | 579 (15.3) | 1,259 (17.5) |
| Anti-aggregants | 379 (11.1) | 312 (8.2) | 691 (9.6) |
| Anti-coagulants | 190 (5.6) | 149 (3.9) | 339 (4.7) |
| Statins | 1,513 (44.4) | 1,544 (40.7) | 3,057 (42.4) |
| Fibrates | 130 (3.8) | 71 (1.9) | 201 (2.8) |
| Anti-inflammatory drugs | 392 (11.5) | 771 (20.3) | 1,163 (16.1) |
| Num. of treatments | 2.5 ± 1.8 | 2.3 ± 1.8 | 2.4 ± 1.8 |
| Glucose (mg/dL) | 113.8 ± 36.1 | 110.7 ± 35.9 | 112.2 ± 36.1 |
| Total cholesterol (mg/dL) | 208.6 ± 43.7 | 211.9 ± 40.4 | 210.4 ± 41.8 |
| Cholesterol LDL (mg/dL) | 130.3 ± 37.4 | 130.0 ± 35.7 | 130.1 ± 36.6 |
| Cholesterol HDL (mg/dL) | 51.2 ± 18.4 | 57.3 ± 19.6 | 54.4 ± 19.3 |
| Triglycerides (mg/dL) | 143.6 ± 74.9 | 131.0 ± 66.3 | 137.0 ± 70.8 |
| Hemoglobin (mg/dL) | 14.6 ± 2.4 | 13.7 ± 2.6 | 14.1 ± 2.5 |
| Creatinine (mg/dL) | 1.0 ± 0.4 | 0.9 ± 0.4 | 1.0 ± 0.4 |
| HbA1c (mg/dL) | 6.6 ± 1.7 | 6.6 ± 1.7 | 6.6 ± 1.7 |
| Potassium (mEq/l) | 4.4 ± 0.6 | 4.4 ± 0.6 | 4.4 ± 0.6 |
| Uric acid (mg/dL) | 6.1 ± 1.7 | 5.2 ± 1.8 | 5.6 ± 1.8 |
| GFR (mL/min) | 87.1 ± 36.4 | 77.0 ± 74.3 | 81.8 ± 59.6 |

* In 312 males and 379 females this data is not available.

**Table III.** GFR estimated by the abbreviated formula from the MDRD study and by the Cockcroft-Gault formula

| GFR category | MDRD | | Cockcroft-Gault* | |
|---|---|---|---|---|
| | N (%) | 95% CI | N (%) | 95% CI |
| < 60 mL/min | 1,531 (21.3) | 20.4-22.2 | 1,528 (22.7) | 21.7-23.7 |
| ≥ 60 mL/min | 5,671 (78.7) | 77.8-79.6 | 5,196 (77.3) | 76.3-78.3 |
| TOTAL | 7,202 (100) | | 6,724 (100) | |

*The GFR value is not available in 478 elements of the sample (6.6%) because of lacking weight or height.

Beta exponentials are shown as adjusted OR with their 95% confidence intervals.

## RESULTS

Data from 9,223 patients are gathered. Geographical distribution of the sample is shown in the map from Figure 1.

*Descriptive study:* Data from 9,223 patients were gathered, of which in 2.021 (21.9%) were considered as not useful for the study since they did not comprised some of the variables necessary for calculation of the main study variable (age, gender, height, weight and creatinine), so that we could evaluate 7.202 (78.1%) patients.

Table II shows the clinical characteristics of study subjects, observing greater age for women than for men, virtually similar BMI, and a higher prevalence of dyslipidemia and ischemic heart disease in men, as well as higher percentage of smokers. About the use of medications, the mean is also higher in men, with differences for higher percentages of use of beta-blockers, alpha-blockers, ASA, statins, and fibrates among men, and higher percentages of use of anti-inflammatory drugs and diuretics among women. In analytical determinations, men have higher mean levels of triglycerides and uric acid, and women have higher mean values of total cholesterol and HDL than men. Finally, we should highlight the higher GFR value in men than women.

*Renal failure (eGF < 60 mL/min/1.73 m$^2$)*: Table III shows the distribution of the estimated GFR both by the abbreviated MDRD study formula and by the Cockcroft-Gault formula. 21.3% by MDRD and 22.7% by CG had eGF < 60 mL/min/1.73 m$^2$.

*Occult renal failure:* We defined occult renal failure as the coexistence of eGF < 60 mL/min/1.73 m$^2$ and normal creatinine, i.e. < 1.1 mg/dL in women and < 1.2 mg/dL in men. With this definition, we found occult CRD in 571 patients, which represents 7.9% of the studied population.

Out of the total number of patients with eGF < 60 mL/min/1.73 m$^2$, the prevalence of occult RF is 37.3%.(95% CI = 34.9-39.7), i.e. more than one third of the patients with renal failure are not detected by determination of plasma creatinine.

The distribution of occult RF by age and gender may be seen in Table IV, which highlights the existence of very significant differences by gender ($p < 0.001$), only finding occult CRD in women , with a very high prevalence (greater than 50%).

By age, we observe higher prevalences in those older than 70 years, as compared with the remaining groups younger than 70 years ($p = 0.01$).

*Univariate analysis with eGF higher or lower than 60 mL/min/1.73 m$^2$:* We used as the main variable the existence of renal failure: eGF ≥ 60 vs. < 60 mL/min, calculated from the abbreviated MDRD formula. Table V shows the percentage of patients with eGF ≥ 60 and < 60 mL/min in relation with the remaining studied variables.

*Socio-demographical characteristics:* About the demographical characteristics, it may be highlighted that it is very significant that women have higher per-

**Table IV.** Prevalence of occult CRD by Age and Gender

| | Occult CRD N (%) | 95% CI |
|---|---|---|
| Age | | |
| < 40 | 7 (30.4) | 11.6-49.2 |
| 40-59 | 115 (31.3) | 26.6-36.0 |
| 60-69 | 175 (30.6) | 33.8-42.8 |
| ≥ 70 | 274 (40.1) | 36.4-43.8 |
| Gender | | |
| Male | 0 (0) | – |
| Female | 571 (53.1) | 50.1-56.1 |

**Table V.** CRD by gender and age

| Variables | GFR ≥ 60 mL/min (%) | GFR < 60 mL/min (%) | p |
|---|---|---|---|
| Gender | | | < 0.001 |
| Male | 86.6 | 13.4 | |
| Female | 71.7 | 28.3 | |
| Age (years) | | | < 0.001 |
| < 40 | 96.5 | 3.5 | |
| 41-60 | 86.1 | 13.9 | |
| 61-70 | 75.8 | 24.2 | |
| 71 and more | 66.3 | 33.7 | |

centage of eGF < 60 mL/min/1.73 $m^{2.}$ (28.3% versus 13.4% in men).

About age, it is very significant that the percentage of eGF < 60 increases as age increases, these very significant differences ($p < 0.001$), by both Pearson's chi-squared and the chi-squared test for trends, being shown in Table V. Indeed, 33.7% of patients older than 70 years attending a Primary Care Center have eGF < 60 mL/min/1.73 $m^2$.

*Renal failure and Associated cardiovascular risk factors:* Table VI shows the relationship between renal function and associated cardiovascular risk factors. We found a significant higher percentage of all studied cardiovascular risk factors in the group with eGF < 60 mL/min, this difference being greater in the groups with AHT and dyslipidemia.

The prevalence of renal failure with eGF < 60 mL/min/1.73 $m^2$ in the different subpopulations is 27.7% within the population with type I diabetes, 26.9% in type II diabetes, 25.2% within the subpopulation with hypertension, 32.7% in dyslipidemic patients, 30.6% in patients with ischemic heart disease, 42.7% in those with a personal history of heart failure, 31.4% in the group with cerebrovascular disease, and 29.4% in the sample with peripheral arteriopathy.

Within the diabetic population, 120 patients had HbA1c values < 7% and glucose < 100 mg/dL, which represents 5.3% of diabetes control out of 2,262 diabetics having both analytical determinations performed.

Within the population with dyslipidemia, 265 patients had cholesterol values < 200 mg/dL and LDL-C < 100 mg/dL and TGC < 150 mg/dL, which represents 7.7% of dyslipidemia control from all dyslipidemic patients.

**Table VI.** Risk factors by group of GFR

| Variables | GFR ≥ 60 mL/min (%) | GFR < 60 mL/min (%) | p |
|---|---|---|---|
| Diabetes Mellitus Type 1 | | | 0.013 |
| No | 97.0 | 95.7 | |
| Yes | 3.0 | 4.3 | |
| Diabetes Mellitus Type 2 | | | < 0.001 |
| No | 73.8 | 64.2 | |
| Yes | 25.2 | 35.8 | |
| AHT | | | < 0.001 |
| No | 36.6 | 21.1 | |
| Yes | 63.4 | 78.9 | |
| Dyslipidemia | | | < 0.001 |
| No | 54.0 | 44.3 | |
| Yes | 46.0 | 55.7 | |
| Ischemic hearth disease | | | < 0.001 |
| No | 91.5 | 86.1 | |
| Yes | 8.5 | 13.9 | |
| Hearth failure | | | < 0.001 |
| No | 96.1 | 89.4 | |
| Yes | 3.9 | 10.6 | |
| Cerebrovascular disease | | | < 0.001 |
| No | 96.9 | 94.7 | |
| Yes | 3.1 | 5.3 | |
| Peripheral arteriopathy | | | < 0.001 |
| No | 95.0 | 92.2 | |
| Yes | 5.0 | 7.8 | |

Figure 2 shows the number of cardiovascular risk factors by eGF higher or lower than 60 mL/min/1.73$m^2$. It may be clearly observed how there is a higher number of patients with GFR higher than 60 with naught or one associated risk factor, whereas the percentage of patients with 2 or more risk factors is greater within the group with GFR < 60. These differences are statistically significant also when using a chi squared test for trends.

*Renal failure and therapies:* Therapies by GFR higher or lower than 60 mL/min may be seen in Table VII:

With the exception of anti-inflammatory drugs, the remaining drugs individually considered are significantly more prescribed in the population with eGF < 60 mL/min. About drugs associations, we observe a greater percentage of patients with no therapy or with mono-therapy in the group with eGF ≥ 60, the percentage being the same for two drugs, and becoming greater for patients having 3 or more drugs in the group with eGF < 60. In this case, this also becomes significant when using the chi-squared test for trends.

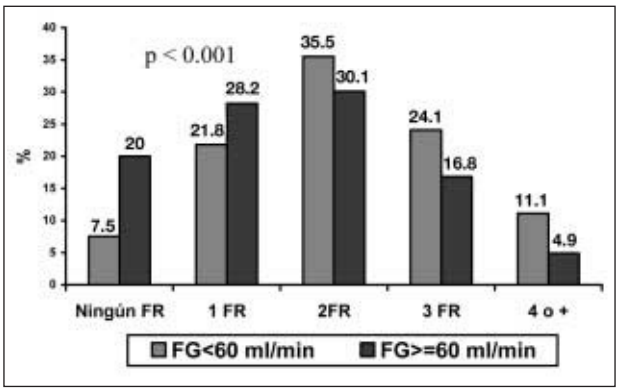


*Fig. 2.—CRD by Num. of CV risk factors and associated cardiovascular pathology.*

*Table VIII shows the data on physical examination by eGF > or < 60 mL/min and by gender. It may be observed a significantly greater BMI in women with eGF < 60 mL/min/1.73 m²:* About smoking status, 12.5% of the smokers have eGF < 60 mL/min, whereas the percentage of non-smokers with this level of eGF is 23.1%, this difference being statistically significant with a p value < 0.001. It may be reminded, however, that only the "current smoker" variable is gathered so that it may happen that there are severe ex-smoker within the group of non-current smokers.

*CRD and Analytical data:* Table IX shows the main statistics of analytical values by eGF level, for both continuous variables and categorized values for each one of them. We always observed higher values in the group with GFR < 60 mL/min but for hemoglobin and HDL-C. In all cases, the differences are statistically significant with the values shown in the Table.

*Crossing CRD with calculation formula:* Table X shows the results from crossing the variable "CRD stage" and the way of calculating glomerular filtration rate, either by the MDRD formula or by the Cockcroft-Gault formula. We observe that disagreements between both are 7.7% for the group with GFR ≥ 60 mL/min and 21.3% for the group with GFR < 60 mL/min.

The sensitivity (0.787) and specificity (0.923) values are quite high, which means that we may very likely deduce which patients will have GFR < 60 mL/min calculated by the Cockcroft-Gault formula if we already know this value when calculating it by the MDRD formula (78.7%).

In order to study the agreement level, we used the Kappa index. Taking into account the Altman's classi-

**Table VII.** Therapies and renal function

| Variables | GFR ≥ 60 mL/min (%) | GFR < 60 mL/min (%) | p |
|---|---|---|---|
| **Current therapies** | | | |
| ACEI | 24.8 | 32.4 | < 0.001 |
| ARA II | 30.8 | 41.2 | < 0.001 |
| Calcium channel blockers | 10.8 | 18.6 | < 0.001 |
| Beta-blockers | 9.8 | 12.2 | < 0.001 |
| Diuretics | 28.0 | 48.8 | < 0.001 |
| Alpha-blockers | 3.7 | 6.1 | < 0.001 |
| Other anti-hypertensive | 1.2 | 2.4 | < 0.001 |
| Oral anti-diabetic drugs | 22.0 | 29.1 | < 0.001 |
| Insulin | 5.4 | 12.0 | < 0.001 |
| ASA | 15.8 | 23.8 | < 0.001 |
| Anti-aggregants | 8.5 | 13.8 | < 0.001 |
| Anti-coagulants | 3.8 | 8.2 | < 0.001 |
| Statins | 39.9 | 52.1 | < 0.001 |
| Fibrates | 2.8 | 2.9 | < 0.05 |
| Anti-inflammatory drugs | 16.3 | 15.7 | < 0.001 |
| Num. of therapies | | | < 0.001 |
| 0 | 17.6 | 5.9 | |
| 1 | 22.2 | 12.1 | |
| 2 | 20.5 | 19.3 | |
| 3 | 16.3 | 21.2 | |
| 4 | 11.7 | 18.0 | |
| 5 or more | 11.6 | 23.5 | |

**Table VIII.** Physical examination by CRD. Mean ± SD

| Variables | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | GFR ≥ 60 mL/min | GFR < 60 mL/min | p | GFR ≥ 60 mL/min | GFR < 60 mL/min | p |
| Weight (kg) | 81.0 ± 12.6 | 80.8 ± 12.7 | 0.679 | 69.9 ± 12.8 | 72.6 ± 12.2 | < 0.001 |
| Height (cm) | 169.8 ± 7.5 | 169.7 ± 7.5 | 0.005 | 159.1 ± 158.7 | 158.7 ± 7.8 | 0.230 |
| BMI (kg/m²) | 28.1 ± 3.9 | 28.4 ± 4.0 | 0.131 | 27.7 ± 5.2 | 28.8 ± 4.7 | < 0.001 |

**Table IX.** Analytical data and CRD

| Variables | GFR ≥ 60 mL/min | GFR < 60 mL/min | p |
|---|---|---|---|
| | Mean ± SD | Mean ± SD | |
| Glucose (mg/dL) | 110.4 ± 35.4 | 118.8 ± 37.7 | < 0.001 |
| Hemoglobin (mg/dL) | 14.2 ± 2.5 | 13.7 ± 2.6 | < 0.001 |
| HbA1c (mg/dL) | 6.5 ± 1.7 | 6.7 ± 1.6 | 0.001 |
| Cholesterol (mg/dL) | 209.6 ± 41.7 | 213.2 ± 42.3 | 0.003 |
| LDL (mg/dL) | 129.6 ± 36.7 | 132.4 ± 36.0 | 0.012 |
| HDL (mg/dL) | 54.9 ± 18.7 | 52.5 ± 21.2 | < 0.001 |
| Potassium (mEq/l) | 4.4 ± 0.6 | 4.5 ± 0.7 | < 0.001 |
| Triglycerides (mg/dL) | 134.5 ± 72.0 | 146.5 ± 65.1 | < 0.001 |
| Uric acid (mg/dL) | 5.5 ± 1.7 | 6.2 ± 2.1 | < 0.001 |
| | % | % | |
| Glucose (mg/dL) | | | < 0.001 |
| < 110 | 65.5 | 54.2 | |
| 110-125 | 12.7 | 15.8 | |
| ≥ 126 | 21.7 | 29.9 | |
| Hemoglobin (mg/dL) | | | < 0.001 |
| < 12 | 5.4 | 12.0 | |
| ≥ 12 | 94.6 | 88.0 | |
| HbA1c (mg/dL) | | | < 0.001 |
| < 6 | 33.1 | 24.7 | |
| ≥ 6 | 66.9 | 75.3 | |
| Cholesterol (mg/dL) | | | < 0.001 |
| < 240 | 78.3 | 73.8 | |
| ≥ 240 | 21.7 | 26.2 | |
| LDL (mg/dL) | | | 0.241 |
| < 160 | 80.9 | 79.5 | |
| ≥ 160 | 19.1 | 20.5 | |
| HDL (mg/dL) | | | 0.029 |
| < 35 | 5.8 | 7.5 | |
| ≥ 35 | 94.2 | 92.5 | |
| Triglycerides (mg/dL) | | | < 0.001 |
| < 200 | 55.1 | 83.4 | |
| ≥ 200 | 14.9 | 16.6 | |
| Potassium (mEq/l) | | | < 0.001 |
| < 3,5 | 4.0 | 5.3 | |
| 3,5-5,1 | 92.7 | 87.0 | |
| ≥ 5,2 | 3.3 | 7.7 | |
| Uric acid (mg/dL) | | | < 0.001 |
| < 7 | 84.3 | 67.9 | |
| ≥ 7 | 15.7 | 32.1 | |

fication,[9] for kappa agreement we obtained a value for the Kappa index of 0.692. This value indicates a good agreement level between both values, which will be kept at this level within the 95% confidence intervals.

*Conditional multivariate logistic regression analysis:* A multiple logistic regression analysis was done including all variables showing significance at the univariate analysis, excluding therapies, and only including the variable "number of therapies". HbA1c values were also excluded since they were only performed in diabetics.

The results are shown in Table XI, by order in which they are entered into the model, i.e. having the lowest p value (higher statistical significance) with regards to the dependent variable (GFR ≥ 60 vs. < 60). The sample size at this point of the analysis is 6,072 (84.3%).

We observe that variables associating with eGF < 60 mL/min are:

- Age, the number of patients with this eGF level increases as the age group increases, and the risk of having low eGF is 1.66 when scaling up from one age group to the next one.
- Gender, with the number of patients with eGF> 60 mL/min being higher in men; a male patient is 3.25 fold more likely of being within this eGF level than a female patient.
- Uric acid, with a higher percentage of eGF < 60 mL/min for the group with uric acid ≥ 7 (mg/dL), the risk being 2.87 times higher for this group.
- The number of treatments registered, the risk for eGF < 60 increasing by 1.29 fold as the number of prescribed medications increases. This negative relationship would be logically explained by the fact that prescription is greater in patients with higher renal dysfunction due to associated cardiovascular risk factors.
- Logically, more patients with eGF < 60 mL/min are comprised in the group with Hb < 12 (g/dL).
- Heart failure: there is clearly more eGF < 60 mL/min within the HF group, the OR being 1.52
- Cholesterol: more eGF < 60 mL/min within the group with a cholesterol level ≥ 240 (mg/dL) , the OR = 1.20.

## DISCUSSION

With this study we aimed at advancing in the knowledge of the real situation of CRD prevalence in our country in those people attending primary health care centers (PCCs) by gathering data from 9,223 patients distributed throughout the entire geographical distribution. The study shows that a great percentage of patients attending PCCs in Spain have CRD stages III-V. Particularly, 21.3% of the patients have this level of CRD. The importance of this study lies on the fact that, apart from being a major predictor of the development of end-stage chronic renal disease, mortality

**Table X.** Crossing CRD according to the formula used to calculate GFR

| | | GFR Cockcroft-Gault | | Total |
|---|---|---|---|---|
| | | > = 60 mL/min | < 60 mL/min | |
| GFR MDRD | > = 60 mL/min | 4,893 | 407 | 5,300 |
| | | 92.3% | 7.7% | 100.0% |
| | < 60 mL/min | 303 | 1,121 | 1,424 |
| | | 21.3% | 78.7% | 100.0% |
| Total | | 5,196 | 1,528 | 6,724 |

is very high in patients with GFR lower than 60 mL/min, mainly due to renal failure-associated cardiovascular complications.[10-12] Early identification of CRD at the primary care setting seems to be important since it will improve management of cardiovascular risk, prevent the prescription of medications affecting renal function, and facilitate referral to the specialist in order to improve long-term care.

In studies performed on general population, not on population attending primacy care centers as ours, the prevalence of stages III-V was 4.7% in the USA[13] and 4.9% in England.[14] In studies carried out by the Spanish Society of Nephrology,[15] the prevalence of glomerular filtration rate < 60 mL/min in the general population was 5.1%.

The most important issue regarding prevention of CRD-associated cardiovascular risk is the not knowing renal function since in most of PCCs and specialized centers the latter is based on the determination of plasma creatinine, a parameter that many times, and particularly in aged women, does not reflect the level of glomerular filtration rate.[16] There lies the importance of one of the issues found in our study, which is the prevalence of the so-called occult renal disease, that is to say, the presence of glomerular filtration < 60 mL/min in patients having normal creatinine value, which is < 1.1/ mg/dL in women and < 1.2 mg/dL in men; we found 7.9% of the studied population with these characteristics. We may highlight that one third of the patients with renal failure were not detected by determining plasma creatinine. In a similar study performed by Duncan *et al* in Canada[17] it was found that 13.9% of the patients having normal plasma creatinine also had glomerular filtration calculated by the Cockcroft-Gault formula < 50 mL/min.

There are some limitations in our study, as well as in the one carried out in Canada. The first one is the fact that these are single cross-sectional studies so that they cannot differentiate between those having transient renal function impairment and those having established CRD. In fact, the definition for these stages states that measurements should be repeated at least three months apart. The second limitation for both studies is the lack of a "gold standard" GFR measurement. Particularly in our case, taking into account that plasma creatinine has been defined at different laboratories with no standardization measurements. Both critics may be compensated considering that the study is just an approach to know with an accepted scattering degree what is the prevalence of this disease at the primary care setting.

What is true is that the prevalence of abnormal renal function is high among patients attending the clinic the PCCs clinics, including many of which have normal plasma creatinine. And the first consequence of this is the importance of introducing in the laboratories a readily accessible measurement such as the MDRD formula to inform primary care physicians and those from specialized care clinics about what patient is the one having an estimated GFR < 60 mL/min.

One of the most important issues on CRD are the data presented by Go *et al*[12] that show that glomerular filtration rate below 60 mL/min/1.73m$^2$ may independently predict the risk for death and cardiovascular events in people with or without known cardiovascular disease and in those submitted to coronary or peripheral artery revascularization. This increase in cardiovascular morbimortality in renal failure patients may be explained not only because CRD is associated with a high number of traditional vascular risk factors but also with particular risks such as mineral metabolism impairments and arterial calcification, endothelial dysfunction, insulin resistance, inflammation, malnourishment, anemia, and several other yet to be defined and clarified. We have found a significant greater percentage of all studied vascular risk factors among patients in the group with GFR < 60 mL/min. The number of cardiovascular risk factors increases with greater loss of glomerular filtration, observing that the percentage of patients with GFR < 60 and two or more cardiovascular risk factors is significantly higher than that of patients with glomerular filtration > 60.

One of the most important issues of identifying CRD at PCCs precisely is the link with cardiovascular risk. Keith *et al*[18] studied 27,998 patients with estimated GFR < 90 mL/min/1.73 m$^2$. They followed their patients for 5 years or until the patients died, were admitted to a Dialysis Unit, or were lost to follow-up. The data from this study showed that with time, 19.9% of the patients were at stage IV CRD, 1.9% at stage III, and 1.3% of those at stage II were on renal

**Table XI.** Multiple logistic regression. Dependent variable: GFR ≥ 60 *vs* < 60

| Independent variable | Beta | OR | 95% CI | P |
|---|---|---|---|---|
| Age<br><40 *vs* 40-49 *vs* 50-69 *vs* ≥ 70 | 0.507 | 1,661 | 1,536-1,796 | < 0.001 |
| Gender (M *vs* F) | -1,179 | 0.308 | 0.265-0.357 | < 0.001 |
| Uric acid<br>< 7 *vs* ≥ 7 (mg/dL) | 1,054 | 2,868 | 2,437-3,376 | < 0.001 |
| Num. of therapies | 0.254 | 1,289 | 1,231-1,349 | < 0.001 |
| Hemoglobin<br>< 12 *vs* ≥ 12 (g/dL) | -0.521 | 0.594 | 0.469-0.752 | < 0.001 |
| Hearth failure<br>(No *vs* Yes) | 0.421 | 1,524 | 1,183-1,962 | 0.001 |
| Cholesterol<br>< 240 *vs* ≥ 240 (mg/dL) | 0.181 | 1,199 | 1,024-1,403 | 0.024 |

replacement therapy. However, the mortality rate was 45.7%, 24.13%, and 19.5%, respectively, concluding that the likelihood of dying was higher than that of entering into a dialysis program, for all stages. In our study, it is clearly shown that there are important cardiovascular risk factors among patients having stages III-IV-V CRD, and thus, we should focus our efforts in reducing mortality in this population by progressing in prevention of coronary heart disease, heart failure, and management of renal failure-associated diabetes and anemia.

We have also studied the number of treatments that patients receive by presence or absence of CRD with eGF < 60 mL/min. There is the conviction that in Nephrology there is some therapeutic nihilism with regards to prescribing drugs that have shown their benefit in patients with cardiovascular diseases with no renal involvement, blaming the lack of prescription to the relatively important contribution of these not controlled cardiovascular factors. However, in this study we have observe a greater percentage of with no therapy or with mono-therapy in the group with GFR > 60 mL/min whereas those having GFR < 60 mL/min were significantly different with regards to drug prescription considering both the percentage of patients treated with each one of cardiovascular protection drugs and the number of associated drugs that they receive. Thus, this study does not seem to show this therapeutic nihilism, or at least it is not so evident. It may be that patients do not adhere to therapies since therapeutic adherence in chronic asymptomatic patients, such as hypertensive patients, is around 50%.[19]

In this study it is also shown that there are laboratory parameters that are particularly impaired in patients having a GFR < 60 mL/min. Independently of diabetic patients, which obviously have a greater degree of renal failure as well as impairments in glucose and glycosilated hemoglobin levels, it should be noted that 12% of the patients with glomerular filtration lower than 60 mL/min had a Hb level < 12 mg/dL as compared to 5.4 % in those with GFR > 60 mL/min. This aspect with Hb is very important taking into account the great impact that anemia has on left ventricular hypertrophy and cardiovascular diseases. It clinically happens that patients with occult renal failure, that is to say with renal failure and normal creatinine, have anemia that is never related with their degree of renal failure. Thus, the importance of early detection of GFR by using these formulas that would allow focusing the anemia diagnosis and its correction, achieving in many of these cases an improvement in quality of life and likely preventing associated cardiovascular complications.

In this study we have shown that there is a series of variables associated with GFR < 60 mL/min. One of them is age. It has been suggested that renal function decreases with time as the aging process progresses.[20] However, according to the Baltimore study which showed a mean decrease of creatinine clearance of 0.75 mL/min per year, a patient having 120 mL/min at the age of 30 years should have more than 80 mL/min at the age of 80 years; so that, identification of patients with CRD and GFR < 60 mL/min, no matter how old they are, does not exclusively represents a physiological aging process but it implies that other associated factors are likely present that may imply complications in the short-intermediate term. We have made it clear in this study. Another variable associated with GFR < 60 mL/min is gender. A male patient is 3.25 times more likely of having GFR > 60 than a female patient.

We have also verified in this study that uric acid determines a greater prevalence of CRD, the risk for having glomerular filtration < 60 being 2.87 times higher in those with uric acid > 7 mg/dL. And this needs an explanation. Hyperuricemia is a very common condition in CRD patients and it does not seem to be harmless. In the studies done by Suliman ME *et al*[21], uric acid levels showed a J association with all mortality causes, being also associated with dyslipidemia, inflammation and impairments in calcium-phosphorus metabolism. This close association between uric acid and cardiovascular and

renal disease has not generally being considered as causative of these diseases. However, there are epidemiological data and clinical studies suggesting that uric acid may contribute to the development of hypertension, metabolic syndrome, and renal disease in some patients. Further clinical studies are needed examining this important possibility, although in our study there is an evidence for the association between uric acid elevation and different degrees of renal failure; it remains to be shown whether or not the former is only due to loss of glomerular filtration.

What is the target population for efficient early detection? Hallan *et al*[22], in the study Hunt II, analyzed in 65,604 adult Norwegian people the incidence of end-stage renal failure and cardiovascular mortality for an eight-year follow-up period. They found that 4.7% had eGF < 60 mL/min/1.73 $m^2$ so that it would be necessary to carry out an appropriate study in 20.6 people in order to detect one case. However, if this study is limited to those people with AHT, diabetes or older than 65 years, then it would be necessary to study 8.7 people to detect one case. In this Norwegian study it was also observed that the relationship with CV mortality is evident and that progression to ESCRD is high (20 %) when eGF is lower than 30 mL/min/1.73 $m^2$, although at 8 eight years of follow-up, the rate of eGF 30-60 mL/min is very low. Thus, the most effective strategy for detection and studies on population with chronic renal disease would be to target the population older than 55 years, hypertensive, and diabetics.

To conclude, this study shows a high prevalence of CRD with estimated glomerular filtration rate lower than 60 mL/min in patients attending primary care centers. As a whole, these patients show greater cardiovascular risk and early detection measures are rendered necessary allowing for greater intervention on this group of patients. The knowledge of this degree of renal function may modify prescription of medications with renal side effects, promote an intervention in those patients needing cardiovascular risk prevention measures, and facilitate early referral to nephrology units, which would allow slowing the disease progression, intensifying cardiovascular protection measures, and ultimately timely designing the selection and preparatory measures for renal replacement therapy.

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