Evaluation of «hidden» renal insufficiency by abbreviated-MRD equation

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SUMMARY

Background: *Early detection of renal insufficiency (RI) allows to start therapies in order to slow renal disease progression and modify associated risk factors. Serum creatinine (Cr) is not a good marker of renal insufficiency. Some patients with significant renal failure can show Cr values in the normal range. Cr derived equations can help us to estimate glomerular filtration rate (GFR) more precisely. The aim of this study has been to know the utility of abbreviated-MDRD equation to detect «hidden» (non detected by Cr) renal insufficiency in patients attending general practices.*

Material and methods: *Patients with blood samples attending general practices in two localities were studied during one year. In all, one thousand patients were included. Collected data were: age, sex, creatinine, haemoglobin, previous diagnosis of arterial hypertension or diabetes mellitus and chronic abuse of analgesic. Abbreviated MDRD equation was used to know GFR. «Hidden» RI was defined when GFR was lower than 60 ml/min/1.73 m^2 and Cr was in the normal range.*

Results: *104 (10.4%) patients showed «hidden» RI. Patients with «hidden» RI were older (70.7 ± 12.5* vs *52.4 ± 18.6 years, p < 0.001), were more frequently women (86.5%* vs *62.4%, p < 0.001) and hypertensive (46.1%* vs *23,6%, p < 0.001) and showed lower levels of haemoglobin (13.8 ± 1.3* vs *14.2 ± 1.3 g/dl, p = 0.001).*

Conclusions: *In patients attending general practices abbreviated-MDRD allows to recognise a significant number of patients with «hidden» renal insufficiency, but with normal range creatinine. Patientes with «hidden» renal insufficiency are more frequently older, women and hypertensive.*

Key words: ***Creatinine. Glomerular filtration rate. Kidney failure. Chronic. Kidney function tests.***

DETECCIÓN DE INSUFICIENCIA RENAL OCULTA EN CONSULTA DE ATENCIÓN PRIMARIA MEDIANTE LA APLICACIÓN DE LA EDUCACIÓN MDRD-ABREVIADA: ANÁLISIS DE 1.000 PACIENTES

RESUMEN

Introducción: *La identificación precoz de los pacientes con insuficiencia renal (IR) permite retrasar la progresión de la enfermedad renal y modificar los factores de riesgo asociados. La creatinina (Cr) puede permanecer dentro del rango normal en algunos pacientes con insuficiencia renal. La utilización de ecuaciones permite estimar mejor el filtrado glomerular (FG). El objetivo de este estudio ha*

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sido intentar conocer cuántos pacientes atendidos en consulta de Atención Primaria tienen insuficiencia renal «oculta» (FG ≤ 60 ml/min/1,73 m²), aplicando la ecuación MDRD abreviada, con creatinina dentro de los límites de rango normal del laboratorio.

Material y métodos: *Estudio de mil pacientes de los que se dispusiera de analítica sanguínea durante 1 año en 2 consultas de atención primaria. Se registraron: edad, sexo, Cr, hemoglobina, presencia de hipertensión arterial, diabetes mellitus y consumo de AINEs. Se utilizó la fórmula abreviada derivada del estudio MDRD, definiendo IR «oculta» cuando el FG era menor de 60 ml/min/1,73 m² y la Cr estaba dentro de los valores de referencia.*

Resultados: *104 (10,4%) pacientes estudiados presentaron IR «oculta». Los pacientes con IR «oculta» tenían mayor edad (70,7 ± 12,3* vs *52,4 ± 18,6 años, p < 0,001), menor hemoglobina (13,8 ± 1,3* vs *14,2 ± 1,3 g/dl, p = 0,001) y eran mayoritariamente mujeres (86,5%* vs *62,4%, p < 0,001) e hipertensos (46,1%* vs *23,6%, p < 0,001).*

Conclusiones: *La utilización de la ecuación MDRD-abreviada en consulta de atención primaria permite detectar un número significativo de pacientes con insuficiencia renal «oculta» entre los pacientes con Cr dentro del rango normal, siendo más útil en pacientes añosos, mujeres e hipertensos.*

Palabras clave: ***Creatinina. Filtrado glomerular. Insuficiencia renal crónica.***

INTRODUCTION

Early detection of patients with renal failure allows initiating therapies that limit the progression of renal damage and modify associated risk factors that contribute to morbidity increase in these patients.[1] Primary care teams play an important role in this detection task. Since in its initial stages renal disease usually is asymptomatic, its identification generally occurs incidentally or by laboratory analysis performed in risk patients, such as hypertensive or diabetic patients.[1] The most commonly used parameter to study renal function is serum creatinine (Cr), but its levels are not above the normal range until there is a significant deterioration of glomerular filtration (GF). Besides, age-associated progressive decrease in muscle mass makes Cr to remain within normal values in spite of the physiological loss of GF. Due to the variability and difficulty of urine collection, creatinine clearance in 24-hour urine samples is, apart from bothersome, inaccurate for estimating GF.[2] Several equations that estimate more accurately GF have been developed, of which the most frequently used one is the Cockcroft-Gault formula.[3] In 1999, Levey *et al*. published several calculations derived from the MDRD (Modification of Diet in Renal Disease) study from GF measured as radio-labeled markers in more than 1600 patients.[4] These calculations have proven to be more accurate to estimate GF in many studies done in a big number of patients, including a recently published European study.[2,5] The main goal of our study was trying to know how many patients seen at the primary care clinic have «hidden» renal failure (GF ≤ 60 mL/min/1.73 m²) with creatinine levels within the normal laboratory range. Defining renal failure as GF below 60 mL/min/1.73m² comes from the fact that, even in elderly patients, this value represent a GF deterioration greater than the «physiologic» one, and because this value of GF increases the risk for progression to chronic renal disease, cardiovascular diseases, anemia, and calcium-phosphorus metabolism impairments.[6] To define GF we used the «abbreviated-MDRD» equation.[2] Our secondary goal was to know the distribution by stages of chronic nephropathy, as defined in the Spanish Society of Nephrology (SEN) guidelines, of patients seen at the primary care clinic.[6]

MATERIAL AND METHODS

We carried out a prospective study of one year duration, from March 31st of 2004 to March 31st of 2005, in two primary care clinics from two different health care areas: the «Plaza del Ejército» Health Care Center at Valladolid, and the «Pintor Oliva» Health Care Center at Palencia. Included patients were all those in whom laboratory work-up

was requested throughout the year (n = 1000; Valladolid 626, Palencia 374). The data gathered the day of the consultation were: gender, age, height, weight, body mass index (BMI), serum creatinine and urea, hemoglobin and hematocrit, previous diagnosis of arterial hypertension (AHT) or diabetes mellitus (DM), and chronic intake of non-steroidal anti-inflammatory drugs (NSAIDS). Patients were considered as being hypertensive if blood pressure was ≥ 140/90 mmHg or they were receiving anti-hypertensive medication.[7] DM was defined as the detection in two occasions of fasting glucose plasma levels ≥ 200 mg/dL or receiving treatment with oral anti-diabetic agents or insulin.[8] Body surface area was calculated according to Dubois's equation: BSA (m^2) = 0.20247 ¥ height (m) 0.725 ¥ weight (kg) 0.4252. GF was calculated according to the abbreviated formula of the MDRD study:

GF (mL/min/1.73 m^2) = 186 × [plasma creatinine (mg/dL)] – 1.154 × (age) – 0.203 × (0.742 if female) × (1.212 if black ethnic origin)] 2.4.

Occult renal failure was considered if the patient presented GF lower than 60 mL/min/1.73m^2 and Cr lower than 1.3 mg/dL, within the laboratory reference limits.[1] Patients were classified according to the stages of chronic nephropathy defined in the Spanish Society of Nephrology Guidelines.[6]

Statistical analysis was done with the SPSS 8.0 software. Mean values were compared by Student's t test, and proportions by the Chi squared test. Results were considered statistically significant when the p value was < 0.05.

RESULTS

Out of 1000 included patients, 44 (4.4%) had serum creatinine above reference limits, whereas 145 (14.5%) had GF lower than 60 mL/min/1.73 m^2. Out of 956 patients with normal creatinine levels, 104 (10.4%) occult renal failure could be detected with GF lower than 60 mL/min/1.73 m^2. When applying the Cockroft-Gault equation, 199 (19.9%) patients had GF < 60 mL/min/1.73 m^2, of which 160 (16%) had creatinine levels within laboratory reference range. When comparing the patients with GF below or above 60 mL/min/1.73 m^2 within the group of patients with normal creatinine, we observed that patients with occult renal failure were significantly older, had lower stature and body surface area, greater BMI, greater serum urine and creatinine, lower hemoglobin and hematocrit, higher AHT prevalence, and were predominantly female patients (table I). There were no significant differences for weight, DM prevalence, or chronic NSAIDS intake (table I).

As shown in Figure 1, as age increases the usefulness of the MDRD equation to detect occult renal failure also increases. Under 50 years of age, 2.2% (9 out of 398) patients had occult renal failure, between ages 50-60 years 6.8% (11 out of 160), between ages 60-70 13.7% (23 out of 167), and above 70 years of age 26.4% (61 out of 231) patients had occult renal failure. Considering the total number of cases included in the study, 23.5% of the patients had stage I chronic nephropathy (GF > 90 mL/min/1.73 m2), 62% were in stage II (GF 60-90 mL/min/1.73 m2), 14.2% were in stage III (GF 30-60 mL/min/1.73 m2), and 0.3% were in stage IV (GF 15-30 mL/min/1.73 m2). We did not detect any patient in stage V (fig. 2).

Table I. Characteristics of the patients with normal creatinine normal according to GF higher or lover than 60 mL/min/1,73 m^2

	EFG* ≤ 60 mL/min/1,73 m^2	EFG* > 60 mL/min/1,73 m^2	p
Age (years)	70 ± 12	52 ± 18	< 0.001
Gender (female)	86.5%	62.4%	< 0.001
Height (m)	1.55 ± 9.54	1.61 ± 10.9	< 0.001
Weight (kg)	68.5 ± 11.0	69.9 ± 14,4	0.349
Body surface area (m^2)	1.67 ± 0.16	1.73 ± 0.19	0.005
BMI (kg/m^2)	28.4 ± 4.6	26.6 ± 4.6	< 0.001
Creatinine (mg/dL)	1.1 ± 0.1	0.8 ± 0.1	< 0.001
Urea (mg/dL)	47 ± 12	36 ± 4	< 0.001
Hemoglobin (g/dL)	13.8 ± 1.3	14.2 ± 1.3	0.001
Hematocrit (%)	41.7 ± 4.0	42.8 ± 3.8	0.006
AHT (%)	46.1%	23.6%	< 0.001
NSAIDS (%)	2.8%	4.3%	0.483
DM (%)	17.3%	14.6%	0.477

DISCUSSION

In this study, we observed that more than 10% of the patients in whom a laboratory analysis is requested at the primary care setting an important reduction in GF can be detected in a simple way. In a prevalence study in the province of Orense, Otero *et al*. detected a 13% prevalence of occult renal failure with GF < 60 mL/min/1.73m^2 using the MDRD equation on 1059 people older than 18 years.[7] Duncan *et al*. detected occult renal failure in 15.2% of 2781 Canadian ambulatory patients using the Cockcroft-Gault formula and a GF threshold of 50 mL/min.[1] Similar findings have been reported in the Spanish population using the Cockcroft-Gault formula.[8] Considering the high amount of patients seen at the primary care clinics, regular application of these equations would supposedly have a great impact in the detection of patients with renal failure. The abbreviated MDRD equation has the advantage of only requiring to know age, gender, and race, besides Cr, to estimate GF. The Spanish Society of Nephrology guidelines recommend to share these data with the laboratory so it can automatically report the estimated GF value besides Cr.[2] In spite of the fact that we detected 14.5% of patients with GF < mL/min/1.73 m^2, these data cannot be inferred to the whole population since this study was not designed to study the real prevalence of renal failure. The most comprehensive studies on renal failure prevalence have been undertaken in the USA using the abbreviated MDRD equation,[29] observing that 4.7% of the population presented GF < 60 mL/min/1.73 m^2. With the Cockcroft-Gault equation, 11.2% of the Australian population is below this value.[10] Currently renal failure prevalence is being studied in Spain with the EPIRCE study (Epidemiology of Chronic Renal Failure in Spain). Previous studies indicate that the number of adult patients with GF < 60 mL/min/1.73 m^2 may be between 7.5% and 17.8%, depending on the methodology used.[6,7,11,12] Patients with normal Cr and low GF were more frequently older and women, and had creatinine and urea values slightly higher, even though within the normal range. Therefore, it is in patients with these characteristics in whom it is more useful to apply the equations to estimate GF. The relationship between age and GF decrease (Figure 1) is clear and is shown in all the studies. In a North American population, the prevalence of GF < 60 mL/min/1.73 m^2 changes from 4.7% for the whole population to 11% in those people older than 65 years non-hypertensive and non-diabetic.[9] In the Spanish population, Gorsotidi *et al*.[11] found a 18.4% prevalence in people older than 60 years (21.1% in our study), and Simal *et al*.[12] of 21.0% in those older than 66 years. With progressive increase of population's age, it is expected that the number of patients with renal disease will increase, so that the application of the equation will be more and more useful as a screening. The greatest usefulness of the equations may be to have an objective parameter of GF decrease that occurs with age. Although we did not observe that in patients with occult renal failure diabetes incidence was higher, we did find a high incidence of other cardiovascular risk factors such as arterial hypertension, overweight, and anemia. Besides being associated with an increase in cardiovascular risk factors, renal failure by itself is being recognized more and more as an independent risk factor.[13] Starting of cardiovascular prevention[6] is recommended wwith a GF < 60 mL/min/1.73 m^2. With the equations, we are able to know patients' GF so that we can categorize them according to chronic renal di-

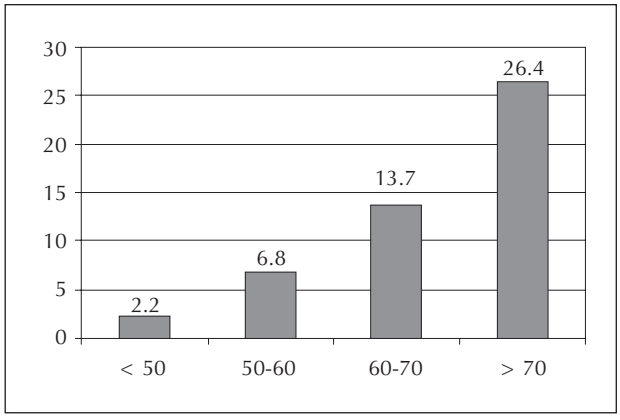

Fig. 1.—Percentage of patients occult renal failure by age groups.

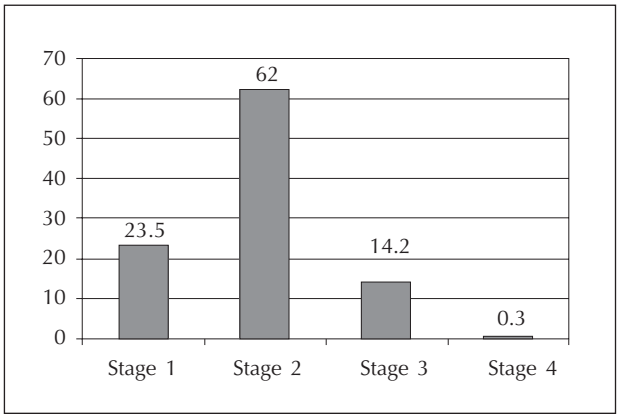

Fig. 2.—Percentage of patients included in each chronic nephropathy stage.

sease stages. In SEN guidelines, a differentiated action plan is proposed for each one of the stages.[6] In spite of not being an epidemiological study, the proportion of patients in stages II and III in our study (62.0% and 14.2%, respectively) was similar to what has been published by Otero *et al*. (59.6% and 12.4%, respectively), and by Simal *et al*. (59.2% and 7.4%, respectively).[7,11] By contrast, in the North American population, only 3% was in a stage II, and 4.3% in stage III.[9] Obviously, these differences may be more due to representativeness of the study selected sample than to population-based differences. In our primary care clinic, both healthy people, which do not receive dialysis and end-stage or sever chronic renal failure patients, which are studied at the hospital, are poorly represented. This makes stages II and III to be more prevalent in our study (fig. 2). To conclude, we would like to highlight that the use of equations to estimate GF at the primary care clinic allows us knowing patients' renal function in a in a simple and better way than only with creatinine, discovering then those patients with «hidden» renal failure. The use of equations is especially useful in elderly patients, female patients, and hypertensive patients.

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