Occult chronic renal disease (OCRD) and associated vascular risk factors (VRF) Epidemiological study

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SUMMARY

Vascular diseases are the first cause of mortality within the occidental world. In Spain, they represent 35.5% within the total of deceases. Vascular diseases, jointly with Diabetic Nephropaty, are the first cause of inclusion of patients in dialysis . In precocious stages of renal disease, and as a consequence of the inflammatory condition generated already exists vascular damage. But its prevention is difficult, because habitually GFR is evaluated by means of plasmatic creatinin rate impeding the suitable detection of renal disease prevailing.

Objective: *The purpose of this study is to evaluate the prevailing of Occult Chronic Kidney Disease (OCKD) and its association with conventional vascular risk factors (VRF).*

Material and Methods: *The epidemiologic study was made in a randomly selected population elder than 18 years. GFR was calculated using Cockcroft-Gault and MDRD methods, and the results were correlated with VRF.*

Results:*The studied population mean age is 50.49 ± 16.28 years, hypertension prevailing is 31.5%, diabetes: 7.5%, obesity: 21,9%, dislipènic: 35,62%, anemia: 1,4%. IV degree IRCO rate (GFR: 15-30 ml/min) is 0.7 (MDRD) with 69.43 ± 12.58 years of age, and 1.5% (C-G) with 76.25 ± 10.64 years of age. GFR, independently on the method used in its calculation, is significantly correlated with TAS (< 0.0001), pulse pressure (< 0,0001), Hb (0,0001), obesity (< 0,0001),Total Cholesterol (< 0,0001), triglycerides (< 0,0018), c-HDL (< 0,0001), c-LDL (< 0,0001) e hiperuricemic (< 0,0001).*

GFR disparity depends on the equation used. It could be explained because C-G overestimate by "weight" and it has higher deviation in lower renal function values. Whereas, using MDRD equation there is an overestimation by "age" and it has lower variability.

Conclusions: *In an aged population, the prevailing of OCKD and the rate of VRF are high conferring high vascular risk. It will be necessary to adopt intervention measures in order to avoid renal disease progress and its high morbid-mortality.*

Key words: Epidemiology. Renal disease. Vascular risk factors.

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ENFERMEDAD RENAL CRÓNICA OCULTA (ERCO), Y FACTORES DE RIESGO VASCULAR (FRV) ASOCIADOS. ESTUDIO EPIDEMIOLÓGICO

RESUMEN

Las enfermedades vasculares son la primera causa de muerte en el mundo occidental, en España representan el 35,5% del total de fallecimientos y son juntamente con la Nefropatía Diabética, la primera causa de inclusión de pacientes en depuración extrarenal. En estadios precoces de insuficiencia renal y como consecuencia del estado inflamatorio que genera, ya existe daño vascular, pero su prevención es difícil ya que de forma habitual se evalúa el GFR mediante la tasa plasmática de creatinina, lo que impide detectar de forma adecuada la prevalencia de enfermedad renal.

Objetivo: *Evaluar la prevalencia de ERCO y su asociación a factores de riesgo vascular (FRV) convencionales.*

Material y metodos: *Estudio epidemiológico, en una muestra aleatoria al azar en una población mayor de 18 años (n = 1059) , se determinó GFR por fórmulas de Cockcroff-Gault y MDRD y se correlaccionó con los FRV.*

Resultados: *La media de edad de la población estudiada es 50,49 ± 16,28 años y la tasa de ERCO Grado III (GFR < 60 ml/min) es 13,1% (MDRD) con una media de edad de 66,27 años y 17,8% (C-G) y edad 68,73 años. El Grado IV (GFR: 15-30 ml/min) es 0,7 (MDRD) con edad de 69,43 ± 12,58 años y 1,5% (C-G) y 76,25 ± 10,64 años. En la población general, la prevalencia de hipertensión es: 31,5%, diabetes: 7,5%, obesidad: 21,9%, dislipemia: 35,62%, anemia: 1,4%. El GFR, independiente del método de medida se correlaciona significativamente con la TAS (< 0,0001), presión del pulso (< 0,0001), Hb (< 0,0001), obesidad (< 0,0001), Colesterol total (< 0,0001), Triglicéridos (< 0,0018), c-HDL (< 0,0001), c-LDL (< 0,0001) e hiperuricemia (< 0,0001).*

La disparidad del GFR en función de la fórmula utilizada es debido a que el C-G sobrestima por peso y tiene una mayor dispersión para valores mas bajos de función renal y MDRD lo hace por la edad, y tiene menor variabilidad.

En conclusión, la prevalencia de ERCO es elevada, en una población envejecida y con tasa elevada de FRV, lo que les confiere un alto riesgo vascular y sería preciso adoptar medidas de intervención a fin de evitar la progresión de la enfermedad renal y su alta morbi-mortalidad.

Palabras clave: Epidemiología. Enfermedad renal oculta. Factores de riesgo vascular.

INTRODUCTION

Prevalence of patients with chronic renal failure with extrarenal depuration is increasing due to an increasing incidence[1], estimated at 12.9% at 10 years, in spite of technical advances in dialysis treatment, and it is presumably due to the fact that 50% of patients have and average of three comorbidity associated risk factors, essentially cardiovascular pathology, as a result of advanced age, an increasing prevalence of diabetic disease and possibly also because of a delayed diagnosis as a result of an insufficient assessment of renal function.

It has been considered that glomerular filtration rate (GFR), measured as inulin clearance,[2] is the best evaluating renal function parameter, although the technique is cumbersome and difficult to apply in daily clinical practice. Then, GFR is assessed through creatinine plasma concentration (Crp) for its easiness and readiness, but it implies different problems such as insufficient urine collection, chromogens that interfere with colorimetric creatinine reaction increasing it up to 20%[3], or reduction of creatinine production due to a decrease in muscular mass in advanced age people in whom, besides GFR decrease that occurs with age, it does not correlate with the increase of plasma Cr,[5] and finally, in the setting of renal failure, an important fraction of plasma Cr is extrarenally excreted and may modify GFR in 2 mL/min in a 70-kg individual.[5,6]

In the general population, Fernández Fresnedo et al.[7] in a sample of 1053 patients and 6451 Crp determinations compared Crp with CrCl measured by

means of the Crockcroft-Gault's formula[8]; in the female group with Crp < 1.1 mg/dL, 22% of them with ages between 60-70 years had a GFR < 50 mL/min, and in male patients with same ages, 11.3% had chronic renal disease, data similar to those reported by others[9,10]; in NHANES III[11], in a sample of 15,625 people, renal disease prevalence in an adult population was 11%.

So that, in clinical practice, GFR must be estimated by mathematical calculations based on Crp, such as Crockcroft-Gault'[8] or MDRD #7, or the abbreviated formula[12], with the exception of special situations such as hyponutrition or musculoeskeletal diseases. When GFR is assessed with more accurate measurements, such as radioactive compounds use (^{99m}Tc-dietylenetriamine-pentaacetic acid) or radio contrast media (^{125}I-iothalamate), the abbreviated MDRD formula is more accurate for GFR calculation than Crockcroft-Gault'.[13]

Mild to moderate renal disease, or occult chronic renal disease (OCRD) is defined as «structural or functional renal impairment and proteinuria with or without a decrease in GFR (< 60 mL/min), or with a decrease in GFR but without any other evidence of renal impairment and does not requires extrarenal depuration».[11] Because of its lack of awareness, this population presents with multiple problems; it comprises a group of people on multiple drugs that seriously interfere with renal adaptation mechanisms and that have a number of comorbidities, essentially vascular, since many of the OCRD complications are established at early phases. With a GFR < 50-60 mL/min, an inflammatory process is initiated: plasma levels of proinflammatory cytokines are increased,[14-16] insulin resistance is increased,[17] adhesion molecules are stimulated,[15] nitric oxide[18] and stem cells[19,20] syntheses are inhibited participating in anemia and left ventricular hypertrophy development.[21] Ultimately, endothelial dysfunction,[22] arteriosclerosis,[23,24] and hyponutrition[21] are induced.

Existent epidemiological data shows it this way. HOT Study[25] demonstrates how Crp greater than 1.3 mg/dL was the most potent predictor for cardiovascular events, and in HOPE Study[26] patients with stage 2 chronic renal disease (Crp < 1.4 mg/dL and GFR: 60-89 mL/min) have a greater incidence of primary cardiovascular events (22.2% vs 15.1%), global and cardiovascular mortality (11.4 vs 6.5%, and 17.8% vs 10.6%), as compared to the population with normal renal function, respectively; these data are similar of those documented at the Framingham study.[27] Recently, Anevakar[28] and Go[29] showed that renal disease is an independent risk factor for death, cardiovascular events, and hospital admission, so that OCRD may considered as a true vascular risk factor (VRF).

Surprisingly, in 1836 Richard Bright[30] described for the first time the relationship between «renal damage» and high blood pressure or hypertension (AHT), considering such «the one that induced growth, cardiac failure and thrombosis». So was initiated a long research track, at the beginning clinical and currently basic, in search for renal disease pathophysiology as a cause of vascular pathology. Given the current knowledge, the epidemiological and clinical data and renal disease pathophysiology indicate that vascular and renal issues are related to each other.

In conclusion, prevalence of «occult» CRF is unknown, and as a result the primary or secondary prevention measures are not applied in order to prevent renal failure progression and development of vascular disease.

OBJECTIVE

To estimate in the general population older than 18 years, the prevalence of «occult» CRF and coexistent VRF.

MATERIAL AND METHODS

Cross-sectional epidemiological study, by means of simple random sampling, and from the electoral roll, a sample of 1059 people was selected from a target population of 328,936, 18 years or older. The sample size has been estimated, with a maximal error attributable to the sample for the least favorable situation of _0.02 for a confidence level of 95%; in order to compensate for losses a 30% greater sample was taken. Selected individuals were appointed by mail to their correspondent primary care center, and specially trained for the study staff traveled to all sampling centers in order to obtain «in situ» all necessary data.

All individuals undergone an epidemiological questionnaire (age, gender, race, and habitat (rural/urban), usual medication consumption, and determination of anthropometrical parameters: blood pressure (right arm; left arm) while sitting with digital manometer, and the mean of three determinations was recorded; weight; height; BMI.

By standard methods the following was determined: hematocrit, hemoglobin, glucose, BUN, Cr, uric acid, total cholesterol (TC), triglycerides (TGC), HDL-Ch and LDL-Ch, GFR calculation by the Cockcroft-Gault's formula and MDRD (simplified formula).

Operative definitions are:

Arterial hypertension[31]

AHT ≥ 140/90 mm Hg
ISAHT (isolated systolic AHT) ≥ 140 mm Hg and < 90 mm Hg
PP (pulse pressure) > 60 mm Hg

Lipids[32]

Hypercholesterolemia: TC > 240 mg/dL or 6.17 mmol/L
Hypertriglyceridemia: TGC > 200 mg/dL or 2.3 mmol/L
LDL Hypercholesterolemia: LDL-Ch > 160 mg/dL or 4.14 mmol/L
HDL Hypocholesterolemia: HDL-Ch < 35 mg/dL or 0.91 mmol/L
Atherogenic index: > 4.5

Cigarette smoking[33]

Ex-smokers: individuals that do not currently smoke but did so for six months or longer in the past.
Non-smokers: those people that have never smoked.
Moderate smokers: < 10 cigarettes/day
Heavy smokers: > 10 cigarettes/day
According to vascular risk studies, as cigarette use increases vascular risk also increases, and there is no low-risk cigarette smoking level.

Alcohol consumption[34]

Defined as the use of alcoholic beverages independently of their alcoholic content.
Quantification of alcohol consumption: mL ± alcohol% ± 0.8 / 100
Non-drinkers
Moderate drinkers: 0.2-69 g/day
Heavy drinkers: > 70 g/day

Obesity[35]

It is assessed according to BMI = weight in kg / height in squared meters
Weighing with electronic scale or balance with minimal 100 intervals and without shoes.
Without overweight
Grade I obesity: BMI: 27-29.9
Grade II obesity: BMI: 30-34.9
Grade III obesity: BMI: 35-39.9
Grade IV obesity: BMI: > 40

Hyperuricemia

Uric acid > 7.5 mg/dL

Diabetes[36]

Plasma glucose > 126 mg/dL or > 7 mmol/L fasting
(Fasting = no calories consumption for the last 8 hours)

Anemia[37]

Hb (men) < 13.5 gr/dL
Hb (women) < 13.5 gr/dL

Renal failure

GFR < 60 mL/min
GFR calculation:
1st- Cockcroft-Gault's formula:[8]
CrCl = (140 – age) × weight (kg) / 72 × Crp (mg/dL/1.73 m^2)
2nd MDRD formula:[12]
GFR = 186.3 × (Plasma Cr)$^{-1.154}$ × (age)$^{-0.203}$
3d- CRF was considered:[11]
Grade 1 = GFR > 90 mL/min and proteinuria
Grade 2 = GFR = 60-89 mL/min
Grade 3 = GFR = 30-59 mL/min
Grade 4 = GFR = 16-29 mL/min
Grade 5 = GFR < 15 mL/min

Habitat

Rural (< 10.000 population); Urban (> 10.000 population)

Statistical methodology

Usual descriptive analysis was performed. For means comparison, Student's t test (for two samples) or analysis of variance (ANOVA) for more than two samples were used, and Chi squared to compare proportions.
The association between quantitative variables was done using Pearson's correlation coefficient.

RESULTS

The final selected sample comprised 1059 individuals (table I), with a mean age of 50.49 years (CI

Table I. Sample distribution and anthropometrial parameters

	Gender		Habitat		
	Men	**Women**	**Urban**	**Rural**	**Total**
n / %	515 / 48.6	544 / 51.4	285	774	1.059
Mean age	48.7 CI = 47.3-50.2	52.17 CI = 50.8-53.5	44.6 CI = 43.2-46.2	52.65 CI = 51.5-53.9	50.49 49.5-51.5
Height	1.679 CI = 1.67-1.68	1.54 CI = 1.54-1.64	1.63 CI = 1.61-1.64	1.60 CI = 1.59-1.61	1.61 CI = 1.60-1.61
Weight	75.9 CI = 74.9-76.9	65.61 CI = 64.7-66.5	70.41 CI = 69.54-71.2	70.43 CI = 69.5-71.2	70.69 CI = 69.8-71.3
BMI	26.9 CI = 26.5-27.2	27.4 CI = 27-27.8	26.7 CI = 26.3-27.1	27.3 CI = 27-27.6	27.18 CI = 26.9-27.4

49.5;51.5). From this sample, 515 are men (48.6%) with 48.71 years (CI: 47.3;50.2) and 544 are women (51.4%), with a mean age of 52.17 (50.8;53.5), significantly higher than male age ($p < 0.001$). About habitat, mean age was higher in rural area than in urban setting (52.65 y.; CI: 51.5;53.9 vs. 44.6; CI: 43.2;46.2; $p < 0.01$).

Mean SBP (systolic blood pressure) is 139.72 mm Hg in men and 138.25 mm Hg in women, until the age of 40-49 years, then they equal, and from 70 years an over it becomes higher in women. According to habitat, it is higher in rural than urban areas (142.69 vs. 128.88 mm Hg; $p < 0.001$). There are no gender differences concerning DBP (diastolic blood pressure): 80.49 mm Hg in men and 79.83 mm Hg in women, and similarly to SBP it is higher in rural areas and in men until the sixties decade.

Mean pulse pressure is 58.29 mm Hg, higher in population older than 69 y., rural areas and with no gender differences.

Mean Hb level was 14.32 gr/dL for the 50-59 years old people and rural women.

Global mean BMI was 27.18, being higher in women: 27.45 vs. 26.90 ($p < 0.05$), rural ($p < 0.001$), and by sex and age it is higher in men until the age of 50, significantly decreasing after the age of 60; the same happens for women although the decrease is milder than for men.

Mean global glucose was 92.96 mg/dL, differences existing men and women (94.59 vs. 91.42 mg/dL; $p < 0.001$), and by age, habitat and gender it is higher in rural men ($p < 0.001$) and for 30-50 years range.

Mean cholesterol level was 224.99 mg/dL, with no differences by gender, although in rural areas it is higher than in urban areas (227.21 vs 216.99 mg/dL; $p < 0.001$), and by age it increases in men until 40 years and then it is higher in women.

Mean triglycerides levels are 135.43 mg/dL, significantly higher in men than women (159.80 vs 112.23 mg/dL; $p < 0.001$). By gender and age, they are higher in men until 40 years of age, and in urban areas vs. rural ($p < 0.001$).

Mean HDL-Ch levels were 56.33 mg/dL, higher in women than in men (60.09 vs. 52.38 mg/dL; $p < 0.001$), with a higher statistical difference in rural than urban habitat (57.05 vs. 54.37 mg/dL; $p < 0.05$), but by gender, both in rural and urban settings, it is greater in women than in men ($p < 0.001$). By age, HDL are not modified until the age of 50-59 years, at which time they start a mild descent until age 69 years ($p < 0.01$), and a significant descent from age 70 and on ($p < 0.05$).

Table II. Anthropometrical and biochemical parameters of the population

	Mean (CI)		Decade	Gender	Habitat
SBP	139.72	(137.5-140.4)	40-49	M	R
DBP	80.49	(79.4-81.1)	50-60	M	R
Pulse pressure	58.82	(57.7-59.8)	> 69	NS	R
Hb g/dL	14.32	(14.2-14.4)	50-59	F	R
BMI	27.18	(26.9-27.4)	NS	F	R
Glucose	92.96	(90.9-94.4)	30-50	M	R
Cholesterol	224.99	(222.2-227.8)	30-40	M	R
Triglycerides	135.43	(128-142.5)	30-40	M	U
HDL-Ch	56.33	(55.4-57.2)	60-70	F	R
LDL-Ch	142.25	(139.87-144.63)	60-70	NS	NS
Uric acid	4.74	(4.6-4.8)	NS	NS	NS
Creatinine	0.96	(0.95-0.97)	> 69	NS	R

M: Male; F: Female; R: Rural; U: Urban.

Table III. Descriptive of VRF in the population

VRF	%	Decade	Gender	Habitat
AHT	31.5	50-59	NS	R(*)
ISAHT	35.3	> 69	M(*)	R(*)
Pulse pressure	48.1	> 69	F(*)	U(*)
Anemia	1.4	50-59	F(*)	R(*)
Obesity	21.9	50-59	F(*)	R(*)
Diabetes	7.52	60-69	NS	R(*)
Hypercholesterolemia	33.24	50-69	NS	R(*)
Hypertrigliceridemia	21.11	40-49	M(*)	R(*)
Hypo-HDL-Ch	3.6	40-49	M(*)	U(*)
Hyper-LDL-Ch	29	50-59	M(*)	U(*)
Hyperuricemia	5.92	40-49	M(*)	NS
AI	35.62	50-59	M(*)	NS
Smoking	24.3	18-39	NS	NS
Alcohol	47.5	30-39	M(*)	NS

NS: not significant; M: Male; F: Female; R: Rural; U: Urban.
(*) = $p < 0.001$

Mean LDL-Ch is 142.25 mg/dL, without any difference by gender or habitat.

Mean uric acid levels in the sample population were 4.74 mg/dL, higher in men than women (5.54 vs. 3.98 mg/dL), without any difference by age, gender or habitat.

Mean plasma creatinine (Crp) was 0.96 mg/dL for people older than 69 years and rural, bur without differences by gender.

Classical VRF prevalence is shown in Table III. 31.5% of the population has high blood pressure, without gender differences: 33.91% of men and 36.33% of women, although more frequent in rural than urban habitat (40.93% vs. 19.51%; $p < 0.001$).

ISHTA was detected in 35.3% of the population, older than 69 years, men, and rural habitat. High pulse pressure was observed in 48% of the people older than 69 years, essentially men and from urban areas.

1.4% of the population had anemia, essentially rural women with ages between 50-59 years.

Obesity was detected in 35.3% of the population, preferentially in women than men (25.32% vs. 18.30%; $p < 0.001$) and it is greater in rural than urban areas (23.94% vs. 16.38%; $p < 0.001$).

Diabetes was demonstrated in 7.52% of the studied population, and was independent of gender (6.92% in men and 8.07% in women) but did vary according to habitat (8.49% in rural areas and 4.88% in urban areas; $p < 0.05$).

Hypercholesterolemia was observed in 33.24% of the population, without gender differences (men 31.38% and women 35.01%), but showing habitat differences (rural 35.50% and urban 27.5%; $p < 0.05$).

Hypertriglyceridemia was present in 21.11% of the population, being more prevalent in men than women (27.17% vs 13.39%; $p < 0.01$), during the 40-49 decade (37.89%; $p < 0.01$), and in the rural setting (21.62% vs 16.03%; $p < 0.05$).

Hypo HDL-Ch was observed in 3.6% of the population, in urban men, 40-49 years old.

Hyper LDL-Ch was detected in 29% of urban men and for the 50-59 decade.

Hyperuricemia was present in 5.92% of the population, and was more prevalent in men than women (10.79% vs 1.20%; $p < 0.01$), essentially for the 40-49 years old decade (21.05%), without habitat differences.

35.62% of the population had an elevated AI, essentially men (44.12% vs 27.52%; $p < 0.001$) until the age of 60 years ($p < 0.001$), without any differences from then on or by habitat.

24.3% were smokers, essentially men (40.46% vs 8.81%; $p < 0.001$), with ages between 18-39 years, but without habitat differences.

47.56% of the studied population consumed alcohol, essentially men (69.36% vs. 26.79%; $p < 0.001$), and decade by decade over women, but without differences by habitat.

In this population, OCRD prevalence is shown in table IV. GFR, measured by C-G formula, was 88.5 mL/min (CI = 86.6-90.4), 100.95 mL/min in men (CI = 98.1-103.1) and 76.6 mL/min in women (CI = 74.5-78.8), and by MDRD was 80 mL/min (CI = 78.9-81), 71.4 mL/min in men and 89.51 mL/min in women.

Table IV. Descriptive of GFR in the population and CORD prevalence by gender

		GFR (C-G)			GFR (MDRD)		
Gender	**N**	**Mean**	**95%CI**	**< 60 mL/min**	**Mean**	**95%CI**	**< 60 mL/min**
M	515	100.9	98.1-103	54 (10.5%)	89.5	87.9-91	18 (3.5%)
F	544	76.6	74.5-78.8	135 (24.8%)	71.4	69.7-72	120 (22.1%)
Total	1.059	88.5	86.6-90.4	189 (17.8%)	80.0	78.9-81	138 (13.1%)

Table V. Distribution of different CORD grades in the study population by two estimation methods

			CRD grade distribution (MDRD)				CRD grade distribution (C-G)
			> = 90	60-89	30-59	15-29	
CORD GRADE (C-G)	> = 90	frecuency	274	209			483
		%(*)	56.7%	43.4%			45.6%
		%(**)	94.5%	33.1%			
	60-89	frecuency	16	347	24		387
		%(*)	4.1%	89.7%	6.2%		36.5%
		%(**)	5.5%	55.0%	18.3%		
	30-59	frecuency		75	98		173
		%(*)		43.4%	56.6%		16.3%
		%(**)		11.9%	74.8%		
	15-29	frecuency			9	7	16
		%(*)			56.3%	43.8%	1.5%
		%(**)			6.9%	100.0%	
CRD grade distribution (MDRD)			290	631	131	7	1,059
			27.4%	59.6%	12.4%	0.7%	100.0%

(*) Patients distribution by different CRD grades according to MDRD for the same CRD grabe by C-G.
(**) Patients distribution by different CRD grades according to C-G for the same CRD grade by MDRD.

Grade III OCRD prevalence (table V) is 17.8% of the population, essentially in women when measured by C-G formula, and mean age is 68.73 years (67.0-70.48), and was 13.1%, also predominantly in women (22.1%), when using the MDRD formula, with a mean age of 66.27% years (CI = 64.04-86.50); grade IV OCRD is 1.5% (by C-G formula) of the population with a mean age of 76.25 years (70.58-81.92) and 0.7% (by MDRD, with a mean age of 69.43 years (57.79-81.06).

Distribution according to OCRD and age is shown in Table VI. As age increases, the rate of renal disease also increases, and as shown in figure 1, and measured by MDRD, when age increases, for the same renal function and Crp values, renal diseases are overestimated, and in relation to weight, (Figure 2), as it increases, renal function, and for the same Crp values, overestimates the C-G formula.

Prevalence of VRF associated to OCRD (Table VII) increases as renal function deteriorates, both when GFR is measured by C-G or MDRD.

AHT increases in relation to GFR both when measured 48/45.5% to 75/85.7% in grade IV CRF ($p < 0.0001$); ISAHT also progresses in the same way, from 29.8/27.9% to 56.3/57.1%, and pulse pressure (from 40.2/40.7% to 68.8/71.4%; $p < 0.0001$), and diabetes (from 7/6.2% to 25/28.8%) ($p = 0.5/0.1$).

Anemia prevalence is greater as GFR decreases, varying from 6.4/7.2% in grade 1 CRF to 12.5/28.6% in grade 4 CRF ($p < 0.0001$). Obesity decreased significantly from 61.9/51.7% to 12.5/28.6% ($p < 0.0001$).

Lipid metabolism also varies according to GFR, especially hypercholesterolemia (from 30.8/25.2% to 31.2/28.6%; $p < 0.0001$); HDL-Ch decreases (from 3.7/3.1 to 6.3/14.3%; $p < 0.0001$), and hypertriglyceridemia levels decreases although not significantly (from 15.3/15.9% to 12.5/14.3%; $p = 0.01/0.954$), and hyperuricemia significantly increases (from 65.4/67.7% to 662.5/85.7%; $p < 0.0001$). The same

Table VI. CORD distribution by age and calculation method

		CORD grade			
Age		> 90	60-89	30-59	15-29
18-39	C-G	74.7%	23.3%	2.0%	
	MDRD	51.4%	47.3%	1.4%	
40-59	C-G	50.2%	43.3%	6.2%	0.2%
	MDRD	25.0%	66.6%	8.2%	0.2%
60-69	C-G	18.4%	49.4%	31.0%	1.3%
	MDRD	11.4%	70.3%	17.1%	1.3%
> 69	C-G	3.9%	28.8%	58.8%	8.5%
	MDRD	4.6%	51.6%	41.2%	2.6%
Total	C-G	45.6%	36.5%	16.3%	1.5%
	MDRD	27.4%	59.6%	12.4%	0.7%

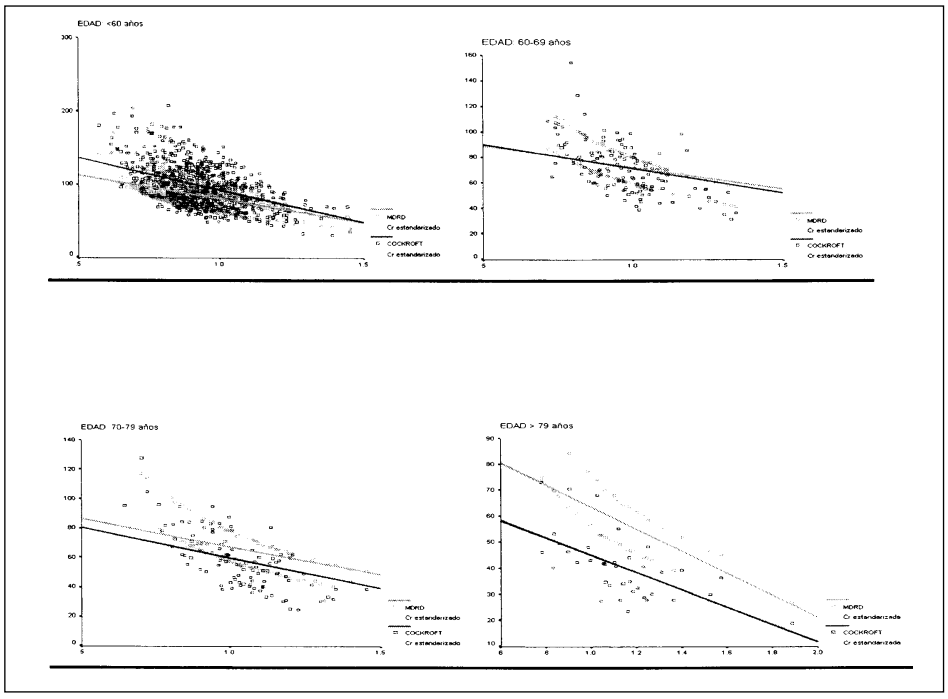

Fig. 1.—Correlation between Crp levels and estimated GFR by both methods (C-G and MDRD): differences by age stratum (as age increases, the C-G method underestimates GFR in relation to MDRD).

happened with alcohol (from 60.9/67.2% to 12.5/0%) and cigarette consumption (from 34.85/43.8% to 9.2/3.1%).

Globally, all conventional VRF were correlated with GFR measured by C-G as by MDRD (Table IX).

DISCUSSION

In the studied population, which mean age (50.49 ± 16.28 years) is slightly higher than the national mean age, the rate of «occult» CRF (GFR < 60 mL/min) varies from 17.8% in the population when the Cockcroft-Gault's formula is used, and 13.1% when MDRD is used. This difference may due to the fact that, for the same Crp levels, C-G's formula overestimates glomerular filtration at the lowest levels[38] up to 23%[39] and, in our case, and for grade IV prevalence, using C-G is 1.5% and using MDRD is 0.7%, which means an overestimation of 43%. For Grade III CORD, C-G formula shows a greater scattering (CI: 86.6-90.4) and, on the contrary, with MDRD it is lower (CI: 78.9-81). Other differences between both formulas are due to the fact that C-G overestimates «weight» and MDRD overestimates «age».

In our population, Grade III CORD rate is 16.3% and Grade IV CORD is 1.5% (C-G) vs. 12.4% and 0.7% (MDRD), respectively, at ages between 76.25 _ 10.64 and 69.43 _ 12.53 years. In a population with 328,936 inhabitants, that means that between 2,302 and 4,934 people have a severe and unknown disease, with a worrisome prevalence of VRF.

It is well known that cardiovascular disease is the greatest death cause in CRF[1,40], and when adjusted by age, it is 30 times higher then in the general population[40], although unfortunately information regarding VRF associated to Grade 2-3 renal disease is scarce, precisely in a population section where preventive measures may have a great benefit.[40] According to our data, AHT rate is 33% in an aged and obese (24.9%) population, with dyslipemia and a

Table VII. Distribution of different vascular risk factors (VRF) in patients with CORD

VRF	GFR (C-G)	< 60 ml/min	GFR (MDRD)	< 60 ml/min
AHT	33.3	26.7-40.5	37.0	28.9-45.6
ISAHT	39.6	32.5-47.0	37.0	28.9-45.8
Pulse pressure	68.8	61.7-75.3	69.6	61.2-77.1
Anemia	8.5	4.9-13.4	8.7	4.6-14.7
Obesity	24.9	18.9-31.7	36.2	28.2-44.8
Diabetes	10.6	6.6-15.9	10.9	6.2-17.3
Hypercholesterolemia	46.0	38.8-53.4	48.6	40.0-57.2
Hypertriglyceridemia	12.7	8.3-18.3	15.9	10.3-23.1
Hypo-HDL-Ch	46.6	39.3-53.9	52.2	43.5-60.7
Hyper-LDL-Ch	1.6	0.3-4.6	2.2	0.5-6.2
Hyperuricemia	22.8	17.4-28.5	19.2	11.7-24.6
AI	29.6	23.2-36.7	39.1	30.9-47.8
Alcohol	8.4	3.8-16.3	2.9	0.3-7.1
Smoking	29.63	23.2-36.7	27.5	20.3-35.8

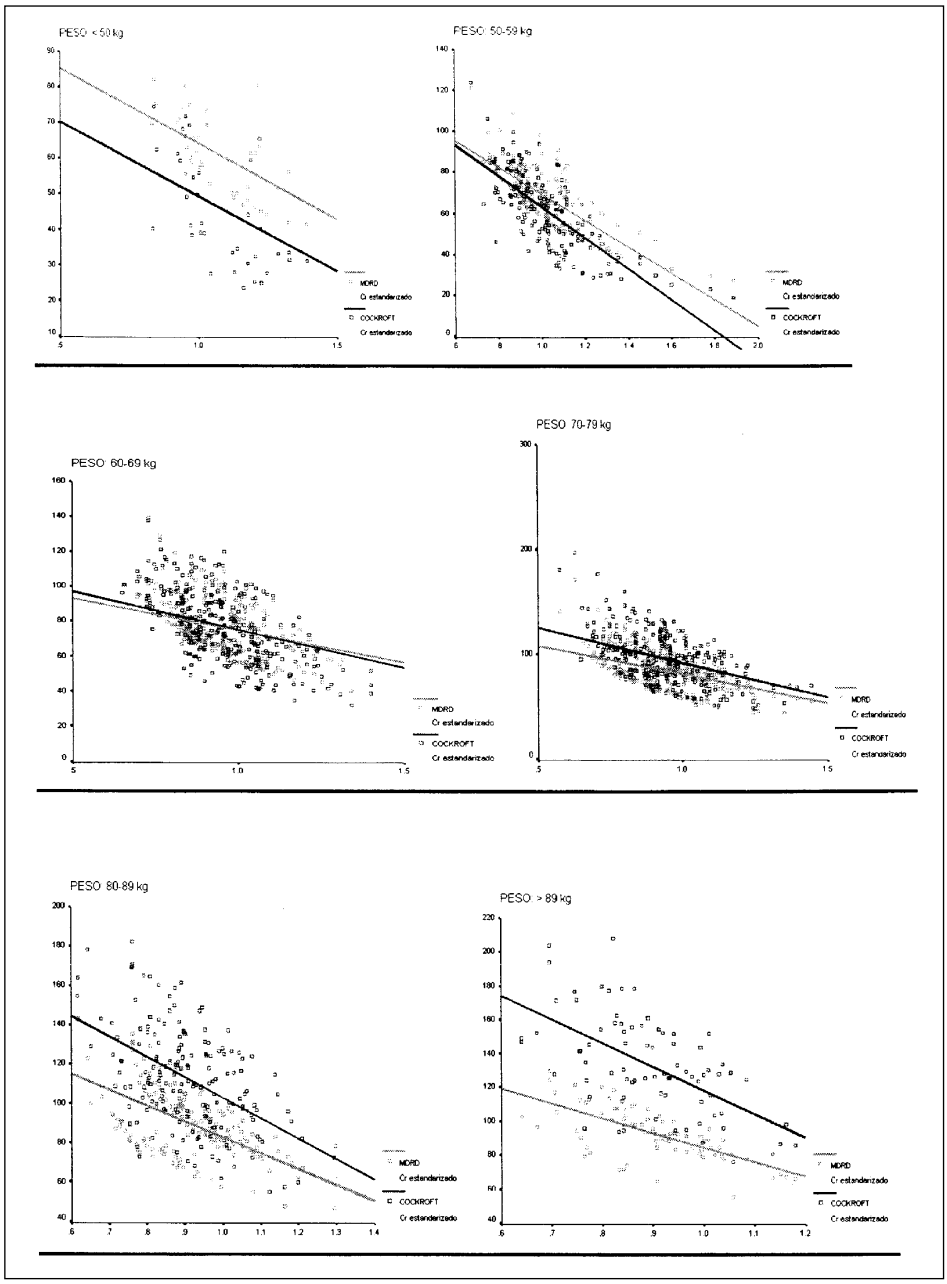

Fig. 2.—Correlation between Crp levels and estimated GFR by both methods (C-G and MDRD): differences by weight (as weight increases, the C-G method overestimates GFR in relation to MDRD).

high cigarette smoking rate (29.6%), and prevalence increases as renal function deteriorates.

Recently, moderate CRF was recognized as a predictor for vascular risk increase in the general population,[29,41-43] and surprisingly, in Framingham's Heart Study[45] it was not shown as a risk factor for the development of cardiovascular events, neither it was in NHANES 1.[45] Later, in the HOPE study[26] 11% of the sample population had moderate renal disease (ClCr < 65 mL/min) and he incidence of the first cardiovascular event was associated with renal function and not with others VRF; the same was demonstrated by Wasnnamethee[46] in a sample of 79,600 people followed for 15 years. In the subgroup of Crp > 1.3 mg/dL, the risk for acute thrombosis was 60% as compared to people with normal Crp.

In patients con arteriosclerotic vascular disease, the incidence of a first vascular event is increased with Crp level, and is independent of traditional VRF[26], and even was not correlated with proteinuria

Table VIII. Distribution of different vascular risk factors (VRF) by CORD grade

VRF		GI	G2	G3	G4
AHT	C-G	48	51.4	76.3	75
	MDRD	45.5	53.2	77.1	85.7
ISAHT	C-G	29.8	32	56.1	56.3
	MDRD	27.9	35.3	50.4	57.1
Pulse pressure	C-G	40.2	47.8	68.8	68.8
	MDRD	40.7	46.8	69.5	71.4
Anemia	C-G	6.4	4.7	8.1	12.5
	MDRD	7.2	5.1	7.6	28.6
Obesity	C-G	61.9	45.0	26	12.5
	MDRD	51.7	50.7	36.6	28.6
Diabetes	C-G	7.0	6.7	9.2	25
	MDRD	6.2	7.4	9.9	28.6
Hypercholesterolemia	C-G	30.8	32.6	47.4	31.3
	MDRD	25.2	35.2	49.6	28.6
Hypertriglyceridemia	C-G	15.3	10.6	12.7	12.5
	MDRD	15.9	11.3	16	14.3
Hypo-HDL-Ch	C-G	65.4	43.9	45.1	62.5
	MDRD	67.6	48.5	50.4	85.7
Hyper-LDL-Ch	C-G	3.7	4.4	1.2	6.3
	MDRD	3.1	4.1	1.5	14.3
Hyperuricemia	C-G	40.7	36.5	21.5	1.3
	MDRD	22.1	56.6	18.6	0.7
AI	C-G	39.1	33.1	28.3	43.8
	MDRD	37.2	33.4	38.9	42.9
Alcohol	C-G	60.9	40.1	31.2	12.5
	MDRD	67.2	43.1	29.0	0
Smoling	C-G	34.8	18.9	9.2	0
	MDRD	43.8	20.0	3.1	0

presence[47], and in a heart failure condition GFR was also an independent predictor factor.[48,49]

In short, all studies demonstrate that moderate CRF is associated with an increased incidence of cardiovascular disease. Manjunath[50] shows how CRF development and within three years, not adjusting for other VRF, prevalence is 40% for GFR of 30 ml/min/1.73 m^2 and 15% when GFR is 130 mL/min. When adjusting for other VRF, for a GFR of 30 mL/min, the risk is 22%, and it still is 15% when GFR is 130 mL/min/1.73 m^2, which demonstrates that GFR decrease is an independent risk factor for vascular disease development.

A limitation for the present study is that, being cross-sectional, it does not allow to clearly establishing the existence of a temporal grade between exposure and outcome. For that reason, that our results are conclusive to establish the causal relationship between renal failure and inflammation-arteriosclerosis. However, current pathophysiological knowledge, together with the outcomes of other experiences, supports this hypothesis.

The increase of vascular risk in CRF patients is due, in part, to the high prevalence of high blood pressure and diabetes. However, other factors, such as homocysteine or dyslipemia, also contribute to it, although the mechanism linking CRF and vascular risk is the existence of an inflammatory state related to renal dysfunction. We know that certain inflammation markers, such as C reactive protein (CRP), fibrinogen, and interleukine-6 (IL-6), are associated with an increase in vascular risk in the healthy population,[51,52] and in CORD the same factors are predictors for mortality. Recently, Shlipak et al.[53], in a large cohort study of 5,888 people and a CRF prevalence of 11%, showed that CRP, fibrinogen, IL-6, Factor VIIc, plasmin-antiplasmin, and D-dimer levels were correlated to the degree of renal function.

The likely pathogenic mechanism (Fig. 3) is linked to renin-angiotensin system (RAS), essentially its main peptide, angiotensin II (AII). The latter is a growth factor and through its AT1 receptor it leads to increased vascular permeability, cellular proliferation, cytokines and extracellular matrix proteins production, arteriolar vasoconstriction, and vascular remodeling. AT1 receptors are coupled to phospholipase C (PLC), and through G proteins, hormone-receptor linkage is followed by a turnover of proteins with guanosine diphosphate (GDP) activity to guanosine triphosphate (GTP). This way, it becomes an allosteric activator of the cascade of cellular enzymes such as mitogen-activated proteins chymases (MAP), and on the other hand, PLC cleaves the membrane phospholipids PIP2 (phosphatidilinositol 4,5 diphosphate), generating two byproducts: 1,4,5-inositol triphosphate (IP3) and diacilglycerol (DAG).

IP3 leads to an increase in free cytosolic calcium and acts as a signaling molecule, linking to calmo-

Table IX. Correlation between VRF and renal function

	GFR (C-G)		GFR (MDRD)	
	Pearson's corr. Coeff.	P	Pearson's corr. Coeff.	p
SBP	-0.201	0.0001	-0.192	0.0001
DBP	-0.035	0.259	-0.102	0.001
Pulse pressure	-0.257	0.0001	-0.195	0.0001
Anemia	0.227	0.0001	0.283	0.0001
Obesity	0.339	0.0001	0.070	0.023
Diabetes	-0.019	0.540	-0.047	0.123
Cholesterol	-0.123	0.0001	-0.180	0.0001
Triglycerides	0.073	0.018	0.002	0.954
HDL-Ch	-0.220	0.0001	-0.149	0.0001
LDL-Ch	-0.106	0.0001	-0.0156	0.0001
AI	0.085	0.006	0.009	0.781
Urid acid	-0.087	0.0001	-0.142	0.001

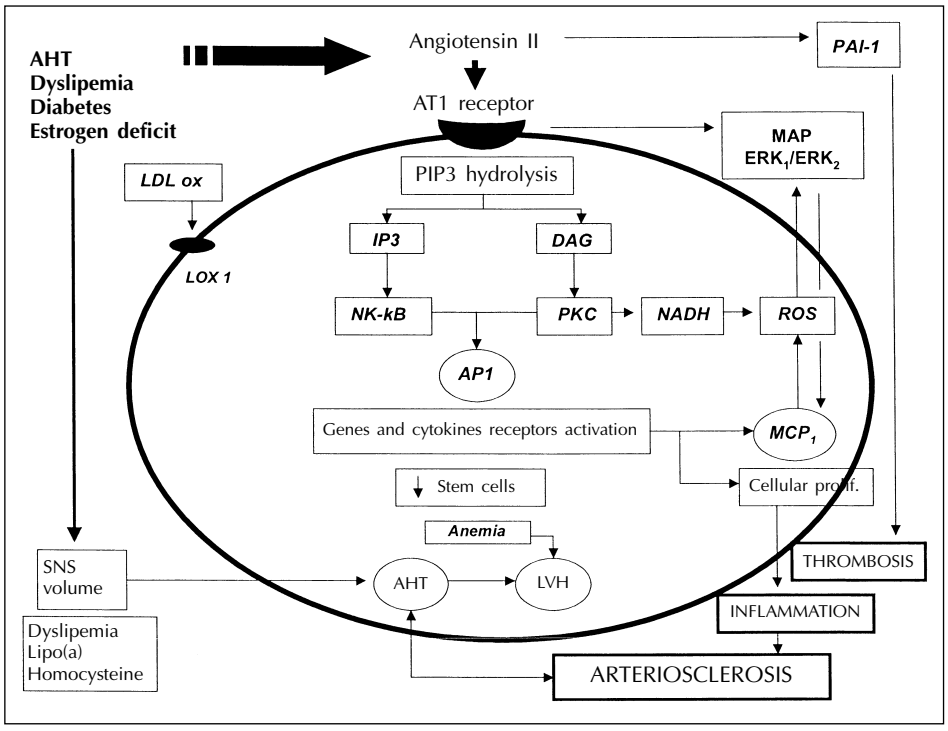

Fig. 3.—Pathophysiology of the inflammatory state linked to CORD.

dulin; Ca-calmodulin complexes activate several enzymes, among which is calcineurin that accounts for nuclear factor κB (NF-κB activation) belonging to the transcription factors family that regulates cytokines, adhesion molecules, angiotensinogen, NO synthase, and cyclooxygenase-2 expression.[54]

DAG is highly hydrophobic and remains within the membrane, but through its high free cytosolic Calcium concentration, it activates membrane-bound PKC that, in turn, activates AP1 (activating protein-1 complexes) and the NADH/NADPH oxidase enzyme,[55] which initiates the oxidative stress generation. ROS (reactive oxygen species) are involved in LDL oxidation,[56] adhesion molecules[57] and MCP1 (monocytes chemotactic protein-1)[58] overproduction, and from a vascular O_2 excess (superoxide anion) and NO deficit, $OONO^-$ (peroxinitrite anion) is produced in excess, which regulates oxidation and nitrosilation reactions; and through H_2O_2 (hydroperoxide) smooth muscle cells growth ensues, finally vascular remodeling.

The cross-linking point for all routes is AP-1, a transcription factors family that link to DNA sequences contributing to the expression of cytokines genes and their receptors genes.

Both in endothelial cells and in smooth muscle cells, AII promotes monocytes adhesion, via MCP1, and their adhesion to endothelial cells through increase of adhesion molecules expression, such as P-selectin, ICAM-1, and VCAM-1,[59] it perpetuates the system since inflammatory cells themselves are able to produce AII, and there is an increase of its receptors.[60] Finally, the loop closes-up when monocytes become macrophages, increasing the expression of oxidized LDL receptors leading to foamy cells.

Another factor is the decrease in the fibrinolitic process. On the one hand, AII stimulates plasminogen inhibitors (PAI-1) without modifying t-PA, and due to the arteriosclerotic process, endothelial and smooth muscle cells produce less plasminogen activators.

On the other hand, in CORD there is a greater neurohormonal activation[61] and sympathetic reactivity as a consequence of a lower NO availability, a natural cathecolamins agonist, and this situation contributes to AHT and left ventricular hypertrophy (LVH) development,[62] although another factor, anemia, adds to LVH development. It is well known how chronic, non uremic, diseases are related to anemia, and the pathogenic mechanism seems to be mediated by proinflammatory cytokines such as IL-1, IL-6, TNF-_ and TNF-_, which abolish erythroid colony forming units (CFU-E) growth[63]; if uremia is added to the inflammatory state, inhibition is greater.[64]

These changes occur early, with a GFR of 70-80 mL/min and in people with essential hypertension.[65]

In conclusion, in the studied sample, occult chronic renal disease prevalence varies from 13% to 17%,

and Grade IV CRF is between 0.7% and 1.5%, which means that for an elderly population and with a high prevalence of conventional risk factors, between 2,302 and 4,934 people have a glomerular filtration rate between 15 and 30 mL/min, which puts them in a high morbidity and mortality situation. It is thus important to adopt simple and early measures to detect CORD in this at risk population in order to decrease renal disease progression and, as a result, mortality.

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