Albuminuria as a Marker of Kidney and Cardio-cerebral Vascular Damage. Isle of Youth Study (ISYS), Cuba

Raúl Herrera MD PhD DrSc, Miguel Almaguer MD, José Chipi MD, Orquídia Martínez MD, Jorge Bacallao MS PhD, Néstor Rodríguez, Miriam de la Caridad Abreu MS, Odeime Fariña MS, María del Carmen Roche MD

ABSTRACT

INTRODUCTION The disease complex comprised of atherosclerosis, chronic kidney disease (CKD) and other associated chronic vascular diseases is the leading cause of mortality worldwide. Microalbuminuria is a marker for vascular damage in the heart, kidney and brain. This paper presents selected findings of the clinical-epidemiological Isle of Youth Study (ISYS) of markers for kidney and vascular damage from chronic vascular diseases and their common risk factors in total population, focusing on Phase 2 reassessment (in 2010) of Phase 1 (2004 to 2006) results.

OBJECTIVES (1) Update the prevalence of risk factors in the study population aged ≥20 years (adult population). (2) Confirm presence of microalbuminuria in at-risk adults diagnosed as presumptive positives in Phase I. (3) Evaluate association between microalbuminuria and selected risk factors.

METHODS Of 3779 adults positive for microalbuminuria in ISYS Phase 1, 73.1% were reevaluated. The risk-factor questionnaire was re-administered and blood pressure, weight and height were measured. Blood was tested for creatinine, glycemia, cholesterol and triglycerides. Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Albuminuria was measured in urine using Micral-Test (Germany) and albumin/creatinine ratio (ACR) by nephelometry. This paper uses ACR as the reference for analyzing risk factor associations. Double-entry tables were developed to analyze association among microalbuminuria, risk factors and co-morbidities.

RESULTS Most prevalent risks were hypertension, consumption of non-steroidal anti-inflammatory drugs (NSAIDs), excess weight and hypertriglyceridemia. Microalbuminuria was confirmed in 18% of cases, using the same test. Elevated prevalence of microalbuminuria was positively associated with advancing age, male sex, underweight, smoking, NSAID use, dyslipidemia, hypertension, diabetes, heart disease and stroke.

CONCLUSIONS The at-risk cohort studied presented low levels of confirmation for positive microalbuminuria. Positive microalbuminuria stratified individuals at greatest risk, except for obesity.

KEYWORDS Chronic kidney disease, cardiovascular disease, risk factors, damage markers, albuminuria, microalbuminuria, Cuba

INTRODUCTION

The association among atherosclerosis, chronic kidney disease and other associated chronic vascular diseases is increasingly well-understood.[1] Atherosclerotic vascular disease is causally related to the group of diseases that comprises the leading cause of global disability, morbidity and mortality. The vascular system is a single entity and damage to it occurs systemically. Risk factors evolve over time, causing progressive vascular damage leading to terminal failure of vital organs. The injury mechanism is the same and depending upon which organ is the most damaged, will manifest as cardiovascular, cerebrovascular, peripheral vascular, or chronic kidney disease, in close relationship to hypertension, diabetes and obesity.[2] The focus of prevention begins with health education and promotion, and continues with the identification of risk groups, stratification of risk and tailored interventions.

Diabetes mellitus and hypertensive vascular disease cause 60–75% of end-stage renal disease (ESRD) worldwide.[3] Chronic kidney disease (CKD) is a strong risk factor for cardiovascular disease (CVD), and this, in turn, is the primary complication and cause of death among CKD patients. Furthermore, cardiovascular mortality is 15 times greater in dialysis patients than in the general population,[4,5] this phenomenon originating in CKD's earliest stages.[6,7]

Over the past decade, this scenario has spurred a change in therapeutic strategies in nephrology, moving from an eminently curative approach focused on ESRD as an individual entity, to a preventive, integrated approach in which CKD is associated primarily with other clinical forms of atherosclerotic vascular disease related to aging. Thus, for example, the journal once titled *Advances in Renal Replacement Therapy* is now called *Advances in Chronic Kidney Disease*.

Accordingly, a high percentage of the population with systemic vascular damage then becomes the focus of prevention, early detection and clinical management, not only by nephrologists, but also by other specialists, including those in primary care, all of whom should address the problem from a cross-disciplinary perspective.

To this end, scientific societies and international health agencies are insisting on the need for population screening, which should be designed and implemented keeping in mind several practical and methodological questions: What is the cost-effectiveness of the population screening? How can developing countries conduct screening? What population should be screened? Which risk factors should be considered? Which markers and methods should be used? Is elevated albuminuria (microalbuminuria) a risk factor or damage marker? Should an isolated finding of microalbuminuria be a criterion for CKD?[8–11]

Positive microalbuminuria is considered not only a marker of renal damage: rather, presence of albumin in urine connotes systemic vascular damage since the kidney is the only vascularized organ that communicates with the exterior through fluid, filtered through its microvasculature.[12] This enables renal disease to be used as a tracer disease, the diagnosis of which reveals other diseases that have vascular damage in common.

Microalbuminuria, arterial intima-media thickening, left ventricular hypertrophy and an elevated coronary calcium score are consid-

ered early markers of permanent damage to vital organs. Microalbuminuria not only predicts the course of CKD, but also of cardiovascular and cerebrovascular disease. According to de Jong and Gansevoort, "Considering CKD in such a way places nephrology at the heart of vascular medicine; it once more emphasizes that the kidney is actually a mirror of the systemic vasculature."[13]

Early detection of microalbuminuria can lead to use of treatments that decrease albumin in urine, improve renal and cardio-cerebral vascular disease prognosis, and reduce the risk of developing diabetic nephropathy.[14] Prevention and treatment in early stages of the disease are imperative.

On Cuba's Isle of Youth, a clinical epidemiological study of total population has been conducted for the past five years, looking at markers of renal and vascular damage from chronic vascular diseases and their common risk factors (Isle of Youth Study, ISYS).[15] With this study, microalbuminuria is being introduced for the first time in the country in population screening for chronic diseases involving atherosclerotic vascular damage.

The Isle of Youth was chosen because it is representative of Cuba as a whole: its health system is the same found throughout the country, and its health indicators are also similar. The latter are comparable to those of developed nations, while the Isle shares socio-demographic and geographic characteristics with other Caribbean islands.

ISYS is divided into four phases:
Phase 1: Active screening for markers of renal and vascular damage, associated risk factors for CKD and related chronic vascular diseases, and determination of glomerular filtration rate (GFR).
Phase 2: Diagnostic confirmation and treatment for patients detected.
Phase 3: Longitudinal follow-up of patients detected and participants testing negative for markers of renal vascular damage.
Phase 4: Intersectoral actions for population health promotion and prevention of CKD and associated chronic vascular diseases.

The present study has the following objectives: (1) Update risk-factor prevalence in the at-risk adult population identified in Phase 1. (2) Confirm presence of microalbuminuria in at-risk adults diagnosed as presumptive positives in Phase I. (3) Evaluate the association between presence of microalbuminuria and risk factors.

METHODS

ISYS Phase 1 was carried out from November 2004 to April 2006, coordinated by the Institute of Nephrology and carried out by the Isle of Youth Municipal Health Department, with the participation of 114 family physicians, 212 nurses and 7 laboratory technicians. Following written informed consent, 96.7% of the total Isle of Youth population (80,117 permanent residents) was studied. Of those, 55,646 were aged ≥20 years (adult study population). Active screening was done via questionnaire administered in a personal interview. Blood pressure, weight and height were measured and body mass index (BMI) calculated. A single first morning urine sample was collected to determine proteinuria and hematuria (Combur-10-Test, Roche Diagnostics GmbH, Germany) for all subjects, and microalbuminuria (Micral-Test, Roche Diagnostics GmbH, Germany) for subjects with renal and vascular risk factors: aged ≥60 years, diabetic, hypertensive, obese, or with a history of cardiovascular, cerebrovascular, or renal disease (15,398 subjects aged ≥20 years). Screening was done by individuals' family physicians and nurses. For those who were positive for any marker of renal and cardiovascular damage, serum creatinine was tested and glomerular filtration rate (GFR) calculated by Cockroft-Gault and Modification of Diet in Renal Disease (MDRD) formulas. The ISYS Phase 1 methodology has been previously published.[16]

Among at-risk adults, 3779 individuals (6.8% of the total study population aged ≥20 years) were found to be presumed positive for microalbuminuria, pending confirmation (based on a second positive test). Individuals determined to be at CKD Stages 3 (6.5%), 4 (0.4%) and 5 (0.1%) were referred for nephrology follow-up. Those at Stages 1 (55.9%) and 2 (37.1%) remained in the care of their family physicians, who were informed of the presumptive positive microalbuminuria.

The present study, part of Phase 2, reports on confirmatory testing for microalbuminuria done in the at-risk cohort aged ≥20 years with presumptive positivity in Phase 1. Five years later, 2762 (73.1%) cases were reassessed (47.4% men; 52.6% women); of the remaining cases, 21.2% were deceased, 46.8% were absent from the municipality when Phase 2 was done, 7.5% refused, 0.2% had begun dialysis and 24.4% missed their appointment. Using methods similar to those described for Phase 1, the risk-factor questionnaire was filled out again, and blood pressure, weight and height were measured. Blood was tested for creatinine, glycemia, cholesterol and triglycerides. GFR was calculated using the MDRD formula and BMI calculated from weight and height. Albuminuria was detected in a first-morning urine sample, using the following techniques:
1) Micral-Test (Roche Diagnostics GmbH, Germany).
2) Albumin/creatinine ratio (ACR), determined by nephelometry. (MININEPH-The Binding Site Ltd., UK).

In Phase 2, all processing of urine and blood samples was done by specialized laboratory personnel in the Central Laboratory at Héroes del Baire Hospital on the Isle of Youth. See Box for a summary of specific variables and parameters used.

Data processing and analysis A Microsoft Access database was created that included a validation system with ranges for each variable to reduce systematic errors. The system automatically calculated age and BMI and performed consistency checks.

Frequency distribution for positive microalbuminuria was calculated for the different methods and equipment used in the study population.

Double-entry tables were used to describe the association of microalbuminuria with the following variables and to calculate odds ratios when possible: age; sex; BMI; blood lipids; smoking; nonsteroidal anti-inflammatory drug (NSAID) use; history of hypertension (HT), diabetes mellitus (DM), cardiovascular disease (CVD), and cerebrovascular disease (CeVD); and blood pressure and glycemia measurements from screening the study population.

Positive ACR values determined by nephelometry were used for the analysis of the association of variables with microalbuminuria.

Phase 2 Variables and Parameters

Variable	Parameters
Chronic kidney disease (CKD) KDOQI-2002 Classification[17]	Estimated glomerular filtration rate <60 ml/min/1.73 m^2 Glomerular filtration rate ≥60 ml/min/1.73 m^2 with kidney damage markers
Cardiovascular disease (CVD)	Physician-documented diagnosis
Cerebrovascular disease (CeVD)	Physician-documented diagnosis
Blood pressure (BP) (in mmHg) JNC7-2003 Classification[18]	Normal: Systolic BP <120 and Diastolic BP <80 Prehypertension: 120–139 or 80–89 Stage 1 HT: 140–159 or 90–99 Stage 2 HT: ≥160 or ≥100
Hypertension (HT)	Physician-documented diagnosis based on prior readings or detected by screening
Fasting glucose (mmol/L) ADA-2003 Classification[19]	Normal: <5.6 Elevated: ≥5.6 and <7 Diabetes: ≥7
Diabetes	Physician-documented diagnosis based on prior measurements or glycemia ≥7 detected by screening
Albuminuria Quantitative: mg/L Albumin/Creatinine Ratio (ACR): mg albumin/g creatinine KDIGO-2004 Classification[20]	Quantitative: (mg/L) ACR(mg/g) Normoalbuminuria: <20 <30 Microalbuminuria: 20–200 30–300 Macroalbuminuria: >200 >300
Age (years)	Age group distribution 20–29 30–39 40–49 50–59 60–69 ≥70
Sex	Male or Female
Body mass index (BMI) (kg/m^2) Quetelet Index[21]	Underweight: <18.5 Normal weight: 18.5–24.9 Overweight: 25.0–29.9 Obese: ≥30
Cholesterol (mmol/L) Coletest method, Carlos J. Finlay Biologicals Production Company (Cuba) (Hitachi 902)	Normal: <6.8 Elevated: ≥6.8
Triglycerides (mmol/L) Monotriglitest method, Carlos J. Finlay Biologicals Production Company (Cuba) (Hitachi 902)	Normal: <1.9 Elevated: ≥1.9
Smoking	Smokers, ex-smokers, and non-smokers
Non-steroidal anti-inflammatory drug (NSAID) use	Yes No

Although the study's objective was eminently descriptive, a logistic regression model was fitted to estimate individual risk for vascular damage as a function of the variables described previously—except for frank cardiovascular or cerebrovascular disease. Using an ROC (receiver operating characteristic) curve, a separability index was estimated for subjects with microalbuminuria confirmed with ACR by nephelometry. After fitting the logistic regression model, a Z-score was calculated for BMI, given the well-known lack of linearity of BMI and risk of CKD. Squared Z-scores were used to account for higher risks at the tails of the distribution. Finally, a regression tree was used to evaluate the gradient for microalbuminuria positivity according to ranges of variation in estimated risk.

RESULTS

Older adults (aged ≥60 years) predominated in the cohort studied in Phase 2. Half of this cohort was hypertensive, and a high percentage regularly used NSAIDs. Two-thirds were overweight or obese, one-third had hypertriglyceridemia, and one-fifth were diabetic (Table 1).

Table 1: Risk Factors in Study Cohort (n = 2762)

Risk Factors	n	%
Hypertension	1372	49.7
Aged ≥60 years	1140	41.3
NSAID use	1084	39.2
Obesity	920	33.3
Overweight	893	32.3
Hypertriglyceridemia	818	29.6
Diabetes mellitus	537	19.4
Smoking	512	18.5
Cardiovascular disease	290	10.5
Hypercholesterolemia	270	9.8
Cerebrovascular disease	84	3.0
Underweight	71	2.6

Using the same Micral-Test in a single urine sample as in Phase 1, persistent microalbuminuria was confirmed in only 18% of cases diagnosed five years earlier as presumptive positives. The distribution of albuminuria was as follows: 10.2% in the 20–49 mg/L range; 4.0% in the 50–99 mg/L range; and 3.6% in the ≥100 mg/L range. Estimated microalbuminuria confirmation in the initial at-risk adult population was 4.4%, or 1.2% of the total adult population screened. Positivity was even lower (2.9% of at-risk adults) when using ARC by nephelometry (Table 2).

Conceptually, all individuals with persistent microalbuminuria are considered to have CKD. The current definition and classification of CKD, proposed in 2002 by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative (KDOQI), says that persistence of microalbuminuria for a period equal to or greater than three months is synonymous with chronic kidney disease.[17]

Analysis of microalbuminuria association with risk markers and factors gave the following results: risk increases monotonically with age; men are at slightly higher risk than women (Table 3). Underweight is the primary risk for positive microalbuminuria, the relationship between weight and risk resembling an inverted J-shape. With quadratic transformation, BMI Z scores show a positive relationship to risk after adjusting for other risk factors, supporting the preceding presumption. Positive microalbuminuria rates were higher in individuals with elevated cholesterol and triglycerides than in those with normal values.

Both smokers and ex-smokers had higher microalbuminuria levels than non-smokers. A similar association was seen in regular NSAID users.

Individuals with a history of hypertension showed a positive microalbuminuria rate of 14.4% compared to 9.7% of those with no such history. Blood pressure readings taken in Phase 2 indicate that as blood pressure rose, so did positive microalbuminuria; even

Table 2: Microalbuminuria Confirmed Cases and Extrapolated Estimates, ISYS Phase 2, by Technique

Technique	Confirmed Cases, Phase 2 (n = 2762) n (%)	Estimated Confirmed, Phase I Adult Presumptive Positive Cases (n = 3779) n (%)	Estimated Positive Cases, Total Adult Population at Risk (n = 15,398) n (%)
Micral Test Roche Diagnostics GmbH, Germany	497 (18.0)	680 (18.0)	680 (4.4)
Albumin/Creatinine Ratio (Nephelometry) The Binding Site Ltd.,United Kingdom	332 (12.0)	453 (12.0)	453 (2.9)

Table 3: Persistent Microalbuminuria in Study Population (n = 2762), by Risk Variable

Risk Variables	Micro-albuminuria negative	Percentage	Micro-albuminuria positive	Percentage	Total (100.0%)
Age					
20–29	168	93.9	11	6.1	179
30–39	331	93.5	23	6.5	354
40–59	989	90.8	100	9.2	1089
60–69	552	84.5	101	15.5	653
≥70	390	80.1	97	19.9	487
Sex					
Male	1142	87.3	166	12.7	1308
Female	1288	88.6	166	11.4	1454
Nutritional Status					
Under-weight	62	87.3	9	12.7	71
Normal weight	661	88.4	87	11.6	748
Overweight	796	89.1	97	10.9	893
Obese	812	88.3	108	11.7	920
Lipids					
Normal cholesterol	2208	88.6	284	11.4	2492
Elevated cholesterol	222	82.2	48	17.8	270
Normal triglycerides	1736	89.3	208	10.7	1944
Elevated triglycerides	694	84.8	124	15.2	818
Smoking					
Non-smokers	1396	89.8	158	10.2	1554
Smokers	600	86.2	96	13.8	696
Ex-smokers	434	84.8	78	15.2	512
NSAID use					
No	1490	88.8	188	11.2	1678
Yes	940	86.7	144	13.3	1084

prehypertension is distinguished from normotension and this is even more pronounced for Stages 1 and 2 hypertension (Table 4). Of subjects diagnosed with diabetes, 20.9% tested positive for microalbuminuria, compared to 9.9% for non-diabetics. Elevated fasting glucose levels were associated with higher microalbuminuria rates, compared to normal glycemia levels, and the rate was even higher for glycemia levels in the diabetic range (Table 4).

A history of ischemic heart disease was associated with higher microalbuminuria positivity rates; this was even truer for history of cerebrovascular disease, at levels greater than diabetes (Table 4).

The presence of any of the chronic atherosclerotic vascular diseases was associated with a greater prevalence of microalbuminuria (Table 4).

The fitted logistic regression model shows the relevance of age, elevated triglycerides and smoking as factors that predispose to microalbuminuria. The large sample sizes may be responsible for the appearance of marginal effects. What is important, nevertheless, is that the model enables estimating an individual risk score that exhibits acceptable separability between positive and non-positive cases (Tables 5, 6).

Furthermore, a regression tree was fitted that shows the properties of this estimated score for determining a clear risk gradient, with positivity distributed as follows (Figure 1):

- <0.08: 5.2%
- 0.08–0.12: 10.7%
- >0.12: 18.7%

Among missing cases (those with a missing value in any of the predictors) the positivity rate was 29.4%.

DISCUSSION

The study cohort was comprised of patients with high prevalence of vascular and renal risk factors. In the general population, the natural evolution of CKD and other chronic atherosclerotic vascular diseases toward their terminal stages has its beginnings in modifiable risk factors that initiate disease and cause it to progress. These factors act synergistically with an individual's personal susceptibility (non-modifiable risk factors).[20] Confirmation of persistent microalbuminuria in this study enabled stratification of population and individuals at risk, an important public health element that permits more efficient and effective use of resources for population health care.

In Phase 2, percentages of microalbuminuria estimated in the total adult population (1.2%) were lower than those obtained in Phase 1 (6.8%). These data reaffirm the need to have at least two positive samples, taken at an interval of at least two weeks, for diagnosis of persistent microalbuminuria.[17] Unfortunately, it was logistically impossible to carry out confirmatory testing within Phase 1. In addition, the difference obtained over several years between samplings may have been influenced by the fact that in Phase 2, all testing was centralized and was performed by specialized personnel, resulting in less inter-rater variability than in Phase I. Studies done on general population samples in other countries, confirmed in shorter time periods, found higher levels than those obtained by this study: AusDiab (Australia): 6.0%;[22] PREVEND (Holland): 7.2%;[23] NHANES III (USA):10.5%.[24]

Table 4: Persistent Microalbuminuria in Study Population (n=2762), by Chronic Vascular Disease

Population					
Variable	Micro-albuminuria negative	%	Micro-albuminuria positive	%	Total (100.0%)
Hypertension (history)					
No	1255	90.3	135	9.7	1390
Yes	1175	85.6	197	14.4	1372
Hypertension (Blood pressure readings)					
Normotension	294	91.0	29	9.0	323
Prehypertension	983	89.0	122	11.0	1105
Hypertension-1	680	88.8	86	11.2	766
Hypertension-2	473	83.3	95	16.7	568
Diabetes mellitus (history)					
No	2005	90.1	220	9.9	2225
Yes	425	79.1	112	20.9	537
Diabetes mellitus (glycemia levels)					
Normal	1856	89.8	210	10.2	2066
High fasting glucose	285	88.5	37	11.5	322
Diabetes	289	77.3	85	22.7	374
Ischemic cardiovascular disease (history)					
No	2192	88.7	280	11.3	2472
Yes	238	82.1	52	17.9	290
Cerebrovascular disease (history)					
No	2367	88.4	311	11.6	2678
Yes	63	75.0	21	25.0	84

Table 5: Logistic Regression Model for Individual Risk of Microalbuminuria (ACR By Nephelometry) by Risk Factor

Variables	BETA	p-value	EXP(BETA)	95% confidence interval	
				Lower	Upper
Hypertension	0.209	0.102	1.233	0.959	1.585
Age	0.027	0.000	1.027	1.019	1.036
Z-BMI[2a]	0.018	0.399	1.018	0.977	1.061
Cholesterol[b]	0.322	0.079	1.380	0.964	1.977
Triglycerides[c]	0.295	0.025	1.343	1.038	1.738
Smoking	0.271	0.045	1.311	1.006	1.708
NSAIDS	0.015	0.908	1.015	0.790	1.304
Constant	-4.527	0.000	0.011		

[a] Squared Z-score of body mass index
[b] Ordinal categorical variable for cholesterol
[c] Ordinal categorical variable for triglycerides

Table 6: Separability Index for Individual Risk Estimated by ROC

Area	Std. Error	p- Value	95% Confidence Interval	
			Lower	Upper
0.647	0.016	0.000	0.615	0.679

Various factors can affect albuminuria measurements. Microalbuminuria is a marker of microvascular damage and systemic inflammation; the latter can be due to acute or chronic inflammatory conditions, including systemic infections, arthritis, colitis, hepatitis, gastritis, dermatitis, fever, heart failure, ketosis, hyperglycemia, hemodynamic stress (such as from exercise) and urinary tract infection. All these conditions can increase albuminuria levels, or skew results from the presence of hematuria or leukocyturia.[10,25] In the study cohort, an attempt was made to reduce to a minimum the influence of these factors. Definitive diagnosis of microalbuminuria should be evaluated over time and based on comprehensive clinical assessment of each patient. However, once microalbuminuria is confirmed, it is of great value in stratification of risk and in determining patient prognosis.

The presence and level of albuminuria have important diagnostic and prognostic significance for CKD and its cardiovascular complications.[26] The KDIGO Controversies Conference (London, 2009) recommended adding ACR (mg/g) (A1: <30; A2: 30–300; and A3: >300) to the CKD staging system.[27,28]

Results of this study confirm progression of atherosclerotic vascular damage parallel to aging and highlight the importance of microalbuminuria for detecting older adults at greater vascular risk. One of the characteristics of the global pandemic of chronic vascular diseases is their greater prevalence at most advanced ages.[29,30] In the United Kingdom, incidence in persons aged >65 years is >350 per 1 million population,[31] while in the United States, in 2007, it was 1687 per 1 million population for the group aged ≥75 years. The mean age of patients who began dialysis in the US that year was 64.7 years.[3]

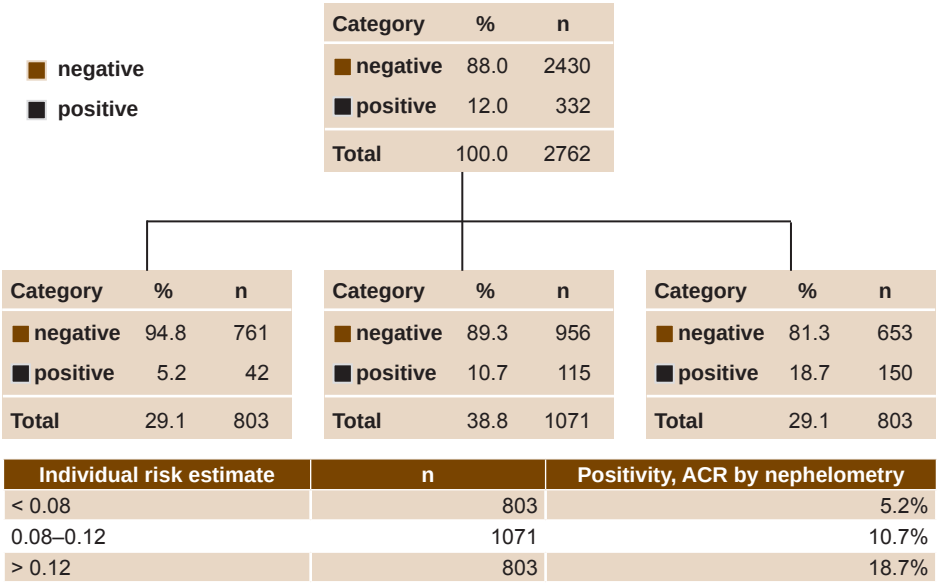
The slightly higher microalbuminuria prevalence in men could be interpreted as evidence of worse evolution, but a more comprehensive assessment of other markers and GFR is needed. Incidence, prevalence and evolution by sex are controversial. In Norway, Eriksen studied disease progression in 58,000 Stage 3 CKD patients for 10 years and found a slower decline in GFR, better evolution and higher renal survival in women than in men.[32] Incidence of dialysis is greater in men than women in the United States,[3] Japan,[33] and also in Cuba.[34] However, in a prospective study of risk factors for CKD in Maryland, USA, the hazard ratio for developing the disease was 2.5 among women compared to 1.4 among men.[35] Glassock refers to research that found a female-to-male ratio of 1.75:1 in Stage 3 CKD.[36] The difference among these studies could be due to differing prevalence of risk factors in the two sexes, primarily of diabetes and hypertension.

Underweight individuals had higher microalbuminuria positivity. One explanation could be that they were older adults who had lost lean body mass, stunted type-1 diabetics, or patients with advanced CKD with accompanying malnutrition. No difference in microalbuminuria prevalence was found between normal weight individuals and those who were overweight or obese, which is not consistent with previous reports.[25]

Vascular and renal damage from dyslipidemia was validated in the study cases by the greater prevalence of microalbuminuria in patients with elevated cholesterol and triglyceride levels. Dyslipidemia is considered one of the traditional risk factors for development of atherosclerosis, cardio-cerebral vascular disease and CKD.[20] Dyslipidemia activates proinflammatory genes that lead to endothelial dysfunction, oxidative stress, inflammation and defective vasodilation of the micro- and macrovasculature.[37]

Smoking produces substances that activate proinflammatory, prothrombotic and vasoconstrictive mediators that accelerate vascular and renal damage.[38] The fact that ex-smokers have a higher rate of positivity than active smokers may be because the ex-smoker group should include older adults and therefore, individuals with greater associated risks. Additionally, clinical practice shows that smoking cessation is more likely among individuals who have had

Figure 1: Regression Tree for Microalbuminuria Positivity and Estimated Individual Risk



Individual risk estimate	n	Positivity, ACR by nephelometry
< 0.08	803	5.2%
0.08–0.12	1071	10.7%
> 0.12	803	18.7%

some adverse health event that has left more extensive vascular injury; in addition, once these vascular lesions are established, their regression is unlikely, even with smoking cessation.

A high proportion of the study population regularly uses NSAIDs and this study shows their vascular-renal toxicity. When renal function is normal, the role of prostaglandin synthesis in maintaining renal hemodynamics is relatively limited. However, when renal perfusion is reduced, as occurs in several forms of cardio-renal disease, dehydration and elderly kidney, adequate renal prostaglandin synthesis becomes the main factor in compensatory activation of renal hemodynamics. In these circumstances, NSAID-induced inhibition of renal prostaglandin synthesis can lead to various renal dysfunction syndromes.[39]

Microalbuminuria exhibits a linear relationship with hypertension as an ordinal indicator. Hypertension is an independent risk factor for cardiovascular disease and for CKD. The frequency of microalbuminuria in study participants was lower than that described in a Spanish study of essential hypertensives (31.3%).[40] The authors point out that microalbuminuria is the renal manifestation of a generalized disorder, characterized by an increase in endothelial permeability, fibrinolysis and coagulation, and the activation of inflammatory processes. Testing for microalbuminuria is the first line for identifying hypertensive patients at high cardiovascular risk, providing the basis for rational use of more expensive therapeutic regimens.

The study cases showed a marked increase in microalbuminuria in the diabetic population and even in individuals with elevated fasting glucose, demonstrating a linear progression of risk. A 15-year follow-up study in the United Kingdom of 4000 diabetics found that 40% of participants developed microalbuminuria and 30% developed renal insufficiency. However, 50% of the latter group did not have preceding microalbuminuria.[41] This suggests that the absence of microalbuminuria does not rule out development of kidney failure among diabetics, because, among other things, diabetics are exposed to other, non-diabetic CKD. This is the reason why the term diabetic nephropathy has been replaced by diabetic renal disease and the term diabetic glomerulopathy has been reserved for demonstration by renal biopsy.[42]

The elevated prevalence of microalbuminuria in patients with a history of ischemic heart disease reflects that albuminuria is a continuous risk for occurrence of cardiovascular events, even below the cutoff points for microalbuminuria.[43] Albuminuria/proteinuria predict cardiovascular and non-cardiovascular mortality in the general population.

Patients with a history of cerebrovascular disease exhibited the highest prevalence of microalbuminuria among all cases studied, which could be an indication that underlying vascular damage is greater. There is a connection between CKD and cognitive phenomena and stroke. The development of cerebrovascular disease is a process involving transition from risk factors for cardiovascular disease, which include CKD, to clinical manifestations of cognitive impairment and stroke. It is suggested that albuminuria and GFR reduction can be used to identify patients who might benefit from more detailed investigations of cognitive deterioration.[44] Risk of dementia increases in the presence of albuminuria. These findings suggest a shared susceptibility for microvascular disease in the brain and kidney in older adults.[45]

CONCLUSIONS

Microalbuminuria is a marker for risk and for early renal and cardiocerebral vascular damage. In the at-risk study cohort, confirmation of microalbuminuria after five years showed low rates of persistence. In cases with persistent microalbuminuria, there was a correlation with all risk factors, except overweight and obesity. Persistent microalbuminuria reveals multiple risk markers and factors. Use of microalbuminuria in screening for chronic kidney disease reveals presence of other chronic atherosclerotic vascular diseases. Persistence of microalbuminuria in patients with vascular risk factors places them at higher risk, indicating early organ damage, which may be reversible. Stratification of risk enables better medical care for patients, more rational use of public health resources, more effective preventive and curative actions, and better orientation of intersectoral measures focused on the individual, the family and the community.

REFERENCES

1. Brown WW. Vascular Disease and Chronic Kidney Disease. Editorial. Adv Chronic Kidney Dis. 2008 Oct;15(4):333–4.
2. Fernández-Britto JE. Aterosclerosis y obesidad. In: Alfonzo JP, editor. Obesidad. Epidemia del siglo XXI. Havana: Editorial Científico-Técnica; 2008. p.175–92.
3. U.S. Renal Data Systems. USRDS 2007 Annual Data Report: Atlas of End Stage Renal Disease in the United States. National Institutes of Health, NIDDK, Bethesda, MD, 2007. Incidence & Prevalence. Am J Kidney Dis. 2010 Jan;55(1 Suppl):S231–40.
4. Bello AK, Nwankwo E, El-Nahas AM. Prevention of chronic kidney disease: A global challenge. Kidney Int Suppl. 2005 Sep;(98):S11–7.
5. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: A new paradigm. Am J Kidney Dis. 2000 Apr;35(4 Suppl 1):S117–31.
6. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks

of death, cardiovascular events, and hospitalization. N Engl J Med. 2004 Sep 23;351(13):1296–305.
7. Ritz E, McClellan WM. Overview: Increased Cardiovascular Risk in Patients with Minor Renal Dysfunction: An Emerging Issue with Far-Reaching Consequences. J Am Soc Nephrol. 2004 Mar;15(3):513–6.
8. Dirks JH, Zeeuw D, Agarwal SK, Atkins RC, Correa-Rotter R, D'Amico G, et al. Prevention of chronic kidney and vascular disease: Toward global health equity–The Bellagio 2004 Declaration. Kidney Int Suppl. 2005 Sep;(98):S1–6.
9. Coresh J, Stevens LA, Levey AS. Chronic kidney disease is common: What do we do next? Nephrol Dial Transplant. 2008 Apr;23(4):1122–5.
10. Stevens LA, Levey AS. Current Status and Future Perspectives for CKD Testing. Am J Kidney Dis. 2009 Mar;53(3 Suppl 3):S17–26.
11. Hallan SI, Stevens P. Screening for chronic kidney disease: which strategy? J Nephrol. 2010 Mar–Apr;23(2):147–55.
12. de Zeew D. Albuminuria, not only a cardiovascular/renal risk marker, but also a target for treatment? Kidney Int Suppl. 2004 Nov;(92):S2–6.
13. de Jong PE, Gansevoort RT. Albuminuria in non-primary renal disease: risk marker rather than risk factor. Nephrol Dial Transplant. 2010 Mar;25(23):656–8.
14. Remuzzi G, Weening JJ. Albuminuria as early test for vascular disease. Lancet. 2005 Feb 12–18;365(9459):556–7.
15. Herrera R, Almaguer M, Chipi J, Toirac X, Martinez O, Castellanos O, et al. Detection of markers of cardiovascular and renal risk in Cuba: Isle of Youth Study (ISYS). Nephron Clin Pract. Forthcoming 2011.
16. Almaguer M, Herrera R, Chipi J, Toirac X, Castellanos O, Bacallao J. Design and methodology of the Isle of Youth community-based epidemiological study of CKD, cardio-cerebral vascular disease, hypertension, and diabetes mellitus (ISYS). MEDICC Rev. 2007;9(1):23–30.
17. Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. National Kidney Foundation: Kidney Disease Outcomes Quality Initiative. Am J Kidney Dis. 2002;39(2 Suppl 1):S7–256.
18. Chobaniam AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. JAMA. 2003 May 21;289(19):2560–72.
19. American Diabetes Association. Standards of medical care in diabetes–2006. Diabetes Care. 2006 Jan;29 Suppl 1:S4–42.
20. Levey AS, Eckardt K, TsukamotoY, Levin A, Coresh J, Rossert J, et al. [Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO)]. Kidney Int. 2005 Jun;67(6):2089–100.
21. Alfonzo JP. Definiciones de sobrepeso y obesidad. In: Alfonzo JP, editor. Obesidad. Epidemia del siglo XXI. Havana: Editorial Científico-Técnica; 2008. p. 175–92.
22. Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, et al. Prevalence of kidney damage in Australian adults: The AusDiab Kidney Study. J Am Soc Nephrol. 2003 Jul;14(7 Suppl 2):S131–8.
23. Hillege HL, Janssen WMT, Bak AAA, Diercks GFH, Grobbee DE, Crijins HJGM, et al. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med. 2001 Jun;249(6):519–26.
24. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of Chronic Kidney Disease and Decreased Renal Function in the Adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003 Jan;41(1):1–12.
25. El Nahas M. Cardio-Kidney-Damage: a unifying concept. Kidney Int. 2010 Jul;78(1):14–8.
26. Glassock RJ, Winearls C. Diagnosing chronic kidney disease. Curr Opin Nephrol Hypertens. 2010 Mar;19(2):123–8. Review.
27. Hogan M. KDIGO Conference Proposes Changes to CKD Classification, but not to the Definition. Nephrology Times. 2009 Dec;2(12):9–10.
28. Burgos-Calderón R, Depine S. Systematic approach for the management of chronic kidney disease: moving beyond chronic kidney disease classification. Curr Opin Nephrol Hypertens. 2010 Mar;19(2):208–13.
29. Abaterusso C, Lupo A, Ortalda V, De Biase V, Pani A, Muggeo M, et al. Treating Elderly People with Diabetes and Stages 3 and 4 Chronic Kidney Disease. Clin J Am Soc Nephrol. 2008 Jul;3(4):1185–94. Epub 2008 Apr 16.
30. Otero A, de Francisco A, Gayoso P, García F; EPIRCE Study Group. Prevalence of chronic renal disease in Spain: Results of the EPIRCE study. Nefrologia. 2010;30(1):78–86.
31. Hamer RA, El Nahas AM. The burden of chronic kidney disease is rising rapidly worldwide. BMJ. 2006 Mar 11;332 (7541):563–4.
32. Eriksen BO, Ingebretsen OC. The progression of chronic kidney disease: A 10-year population-based study of the effects of gender and age. Kidney Int. 2006 Jan;69(2):375–82.
33. Iseki K. Screening for renal disease—what can be learned from the Okinawa experience. Nephrol Dial Transplant. 2006 Apr;21(4):839–43. Epub 2006 Feb 16.
34. Registro Estadístico de la Oficina del Centro Coordinador Nacional del Programa Enfermedad Renal Crónica, Diálisis y Transplante Renal. Instituto de Nefrología. Havana: Ministry of Public Health (CU); 2009.
35. Haroun MK, Jaar BG, Hoffman SC, Comstock GW, Klag MJ, Coresh J. Risk factors for Chronic Kidney Disease: A Prospective Study of 23,534 Men and Women in Washington County, Maryland. J Am Soc Nephrol. 2003 Nov;14(11):2934–41.
36. Glassock RJ, Winearls C. An epidemic of chronic kidney disease: fact or fiction? Nephrol Dial Transplant. 2008 Apr;23(4):1117–21.
37. Wanner C, Ritz E. Reducing lipids for CV protection in CKD patients—current evidence. Kidney Int Suppl. 2008 Dec;74(111):S24–8.
38. Orth SR. Smoking—a renal risk factor. Nephron. 2000 Sep;86(1):12–26.
39. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med. 1999 May 31;106(5B):13S–24S.
40. Segura J, Campo C, Ruilope LM. Effect of proteinuria and glomerular filtration rate on cardiovascular risk in essential hypertension. Kidney Int Suppl. 2004 Nov;(92):S45–9.
41. Mann JF, Yi QL, Gerstein HC. Albuminuria as a predictor of cardiovascular and renal outcomes in people with known atherosclerotic cardiovascular disease. Kidney Int Suppl. 2004 Nov;(92):S59–62.
42. Atkins RC, Zimmet P. Diabetic Kidney disease: act now or pay later. Kidney Int. 2010 Mar;77(5):378–80.
43. Levin A, Rocco M. Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Am J Kidney Dis. 2007 Feb;49(2 Suppl 2):S13–9.
44. Weiner DE. The Cognition-Kidney Disease Connection: Lessons From Population-Based Studies in de United States. Am J Kidney Dis. 2008 Aug;52(2):201–4.
45. Barzilay JI, Fitzpatrick AL, Luchsinger J, Yasar S, Bernik C, Jenny NS, et al. Albuminuria and Dementia in the Elderly: A Community Study. Am J Kidney Dis. 2008 Aug;52(2):216–26.

THE AUTHORS

Raúl Herrera Valdés (Corresponding author: raul.herrera@infomed.sld.cu), nephrologist. Full professor and distinguished researcher, Medical University of Havana and Nephrology Institute, Havana, Cuba.

Miguel Almaguer López, nephrologist. Associate Professor and Senior Researcher, Medical University of Havana, Havana, Cuba. Chief of the Preventive Nephrology Department, Nephrology Institute, Havana, Cuba.

José Chipi Cabrera, nephrologist. Associate Professor, Héroes del Baire Hospital, Nueva Gerona, Isle of Youth Special Municipality, Cuba.

Orquídia Martínez Soto, nephrologist. Chief of the Nephrology Service, Héroes del Baire Hospital, Nueva Gerona, Isle of Youth Special Municipality, Cuba.

Jorge Bacallao Gallestey, mathematician and biostatistician. Full professor, Medical University of Havana, Atherosclerosis Research and Reference Center, Havana, Cuba.

Néstor Rodríguez Triana, information technologist. Information Technology Department, Héroes del Baire Hospital, Nueva Gerona, Isle of Youth Special Municipality, Cuba.

Miriam de la Caridad Abreu Correa, clinical laboratory scientist. Adjunct professor, Héroes del Baire Hospital, Nueva Gerona, Isle of Youth Special Municipality, Cuba.

Odeime Fariña Martínez, clinical laboratory scientist. Instructor, Héroes del Baire Hospital, Nueva Gerona, Isle of Youth Special Municipality, Cuba.

María del Carmen Roche Gutiérrez, specialist in family medicine and clinical laboratory science. Instructor, Héroes del Baire Hospital, Nueva Gerona, Isle of Youth Special Municipality, Cuba.

Submitted: August 27, 2010
Approved for publication: October 10, 2010
Disclosures: None