



## ORIGINALS

# *Proteinuria and chronic renal failure in the coast of El Salvador*

R. Gracia-Trabanino\*, J. Domínguez\*\*, J. M. Jansà\*\*\* and A. Oliver\*

\*Puigvert Foundation. Universidad Autónoma de Barcelona. \*\*Social Fund for Health Emergency, coast zone. Usulután. El Salvador. \*\*\*Barcelona Public Health Agency.

### SUMMARY

**Objectives:** *El Salvador has high mortality rates from chronic kidney disease (CKD). The actual prevalence and causes remain unknown and local resources are scarce. Previous studies have suggested very high prevalence in specific populations: adult male farmers living in the coastlands, with high frequency of pesticides exposure and alcohol consumption. This population has low incomes and poor healthcare accessibility. Our aim was to detect CKD cases in this population using proteinuria as an inexpensive initial screening, investigating associations with those characteristics and comparing them with another population from the midlands.*

**Methods:** *We performed a transversal study on volunteer men from both regions, taking into consideration the variables: age, farmer living, pesticides, exposure, alcohol consumption, medical past history, blood pressure level, glycemia and proteinuria in a random urine sample. Coastland men with proteinuria were additionally screened for CKD measuring hemoglobin and serum creatinine levels. Finally, we employed a logistic regression model, and Pearson's  $\chi^2$  to investigate associations between those variables and the presence of proteinuria or CKD.*

**Results:** *We included 291 men from the coastlands and 62 from the midlands: 35 and 16% off the total male population from their respective communities. Proteinuria (table I) was found in 133 (45.7%) and 8 cases (12.9%). CKD was diagnosed in 37 (12.7%) coastland men (table III), with mean creatinine  $2.64 \pm 2.5$  mg/dl, hemoglobin  $12.32 \pm 1.9$  g/dl and 81.1% with proteinuria 15-30 mg/l. Only 14 (37.8%) out of those 37 CKD patients featured diabetes or hypertension, while the remaining (62.2%) did not appear to have a clear-cut cause for CKD.*

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**Correspondencia:** Dr. Ramón Gracia-Trabanino

Unidad de Trasplantes

Fundación Puigvert

Cartagena, 340

08025 Barcelona

Only one of them was formerly diagnosed with CKD. Farmer living, pesticides exposure and alcohol consumption were found to be very common characteristics in both populations, and were not associated to the presence of proteinuria or CKD (table II and III).

**Discussion:** The prevalence of CKD within the adult male farmers from the Salvadoran coastlands is remarkably high: at least 12.7%. There is a large number of undiagnosed cases, but they can be easily detected with inexpensive methods. This high prevalence is not completely explained by usual CKD causes like diabetes or hypertension. In addition, pesticides exposure and alcohol consumption may not be related, too. The disease is moderate, non symptomatic and has fairly mild proteinuria, possibly from interstitial origin. Further research is required to investigate environmental, occupational and hereditary factors, and to determine the real extent of the problem.

Key words: **El Salvador, chronic kidney disease, proteinuria, prevalence, alcohol, pesticides.**

## PROTEINURIA E INSUFICIENCIA RENAL CRÓNICA EN LA COSTA DE EL SALVADOR: DETECCIÓN CON MÉTODOS DE BAJO COSTO Y FACTORES ASOCIADOS

### RESUMEN

**Objetivos:** El Salvador tiene alta mortalidad por insuficiencia renal crónica (IRC), hay poca información y los recursos son escasos. Estudios previos sugieren alta prevalencia en poblaciones con características específicas: varones agricultores de zonas costeras con exposición a pesticidas y etilismo frecuente. Nuestro objetivo fue detectar casos de IRC en esta población utilizando proteinuria como cribado inicial económico, investigando asociaciones con tales características y comparándolos con otra población alejada de la costa.

**Métodos:** Realizamos un estudio transversal en varones voluntarios de ambas regiones considerando: edad, ocupación agrícola, exposición a pesticidas, etilismo frecuente, antecedentes médicos, presión arterial, glucemia y proteinuria en muestra al azar. En proteinúricos de la costa medimos hemoglobina y creatinina sérica buscando IRC. Investigamos asociación de proteinuria e IRC con estas variables dependiendo empleando un modelo de regresión logística y prueba de Chi<sup>2</sup>.

**Resultados:** Incluimos 291 varones de la costa y 62 de la zona alta: 35 y 16% del total de sus comunidades, respectivamente. Presentaban proteinuria 133 (45,7%) y 8 (12,9%) casos. Diagnosticamos IRC a 37 (12,7%) varones de la costa, con creatinina  $2,64 \pm 2,5$  mg/dl, hemoglobina  $12,32 \pm 1,9$  g/dl y un 81,15 con proteinuria 15-30 mg/l. Solamente 14 (37,8%) presentaban diabetes y/o hipertensión, los demás (62,2%) sin etiología clara. Sólo uno estaba previamente diagnosticado. Ser agricultor, la exposición a pesticidas y el etilismo frecuente resultaron características muy comunes y no predictoras ni asociadas a presentar proteinuria o IRC.

**Discusión:** La prevalencia de IRC en varones agricultores de la costa es muy alta: 12,7% como mínimo, pero fácilmente detectable con métodos económicos sencillos. Etiologías habituales, diabetes e hipertensión, no explican tal prevalencia. La exposición a pesticidas y el etilismo tampoco parecen relacionados. La IRC es generalmente moderada, asintomática y poco proteinúrica, de posible origen intersticial. Deben

*conducirse estudios más amplios investigando factores ambientales, ocupacionales y hereditarios.*

Palabras clave: ***El Salvador, insuficiencia renal crónica, proteinuria, prevalencia, alcohol, pesticidas.***

## INTRODUCTION

A previous study<sup>1</sup> undertaken at a third level nephrologic center has begun to reveal the peculiar situation of chronic renal failure (CRF) at El Salvador. Many questions have been raised but little is known about the etiology and epidemiologic matters of the disease, no updated information is available and mortality from this cause is high<sup>2</sup>. In that study<sup>1</sup> it could be observed that most of CRF patients come from specific areas of the country and share a common epidemiologic profile: they are men (87.4%) farmers (75%) with a mean age of  $51 \pm 16$  years, with a high rate of locally distilled alcoholic beverages intake (72.6%), and live in coastline zones that until several decades ago were cotton plantations where frequent exposure to weed killers and pesticides (73.3%) has been and still is a usual fact<sup>1,3</sup>. Arterial hypertension, diabetes, glomerulopathies and other traditionally recognized entities for CRF etiology<sup>4</sup> did not explain the majority (66.8%) of these cases<sup>1</sup>. The forementioned area is mainly agricultural, inhabited by very low-income farmers without social security. Its basic diet consists in grains, mainly corn and red beans, and coffee. Women tend to spend their time in housework and men provide the financial support to the family group, working long hours on the fields under the sun, usually with an inadequate fluid intake.

To begin gathering more information about the problem, it was decided to study those men *in situ*, in one of the places of origin most frequently reported in the hospital-based study<sup>1</sup>: the Jaquilisco zone, in the Pacific Ocean coast of El Salvador.

The goal of the study was to diagnose CRF cases in coastline men using proteinuria as a cheap initial screening and to study the demographic, clinical and basic analytical related factors, and comparing them with another population far away from the coast, using simple and low cost methods.

## MATERIAL AND METHODS

After presenting the method to local communities,

a low cost, simple, observational and cross-sectional study was performed, with a random sample using the random voluntary participation criterion, in two consecutive phases.

In the first phase, a young men adult sample of the coastline zone of Jaquilisco was studied, using as control another population with similar demographic characteristics, living in higher lands at Satori zone, some 500 meters above sea level. In all of these young adult males of both regions, a personal questionnaire was done gathering the following information: place of residence (coast or high zone), age, occupation in agricultural work, history of pesticides exposure, frequent consumption of alcoholic beverages, and basic medical history. In all patients, arterial blood pressure, peripheral capillary glucose levels, and presence of proteinuria by means of random urine reactive deep stick were measured. We used the presence of proteinuria as a screening method to select study cases since it is a basic and low cost indicator of renal injury.

In the second phase, the male coastline participants with proteinuria were offered the possibility to perform basic laboratory analyses: hemoglobin (Hb) and serum creatinine, to detect CRF cases.

Peripheral capillary glucose levels were measured with Accu-Check<sup>®</sup> Sensor system, with a  $99.5 \pm 3\%$  accuracy rate. In order to control for the proteinuria deep sticks Multistix<sup>®</sup> 10SG, a small random sampling was done apart in some voluntary adult women from the same coastal communities. Detections for proteinuria and glucose cost \$1 per person and creatinine and Hb \$5.40. The study was privately funded with funds coming from the same communities and external contributions, by means of the Social Fund of Emergency of Jaquilisco (base Organization) and the Barcelona Public Health Agency, Spain.

As diagnostic criteria for CRF, simple parameters such as diabetes mellitus (DM) and arterial hypertension (AHT) were used, respectively: serum creatinine equal or higher to  $1.5 \text{ mg/dL}$ <sup>5</sup>, glucose level fasting greater than  $126 \text{ mg/dL}$ <sup>6</sup>, and arterial blood pressure greater than 140/90 mmHg.

Statistical analysis: Results are expressed as means

**Table I.** Characteristics and prevalence of proteinuria in adult men in two zones of El Salvador

	Coastline zone*	High-lands zone**	P
Total studied cases	291 (100%)	62 (100%)	
Age in years:	50.2 ± 15.9	54.8 ± 9.6	0.003
Older than 60 years	93 (32%)	18 (29%)	0.386
Farmers:	250 (85.9%)	57 (91.9%)	0.140
Exposure to pesticides:	234 (80.4%)	53 (85.5%)	0.230
Alcoholism:	189 (65.0%)	54 (87.1%)	< 0.0005
DM***:	73 (25.1%)	5 (8.1%)	0.006
AHT***:	42 (14.4%)	16 (25.8%)	0.045
Proteinuria****:	133 (45.7%)	8 (12.9%)	< 0.0001

\* Rural communities of Jaquilsco region, in the Pacific Coast.

\*\* Rural communities of Sesorí region, inland, 500 meters (approx.) above sea level.

\*\*\* Provisional diagnoses.

\*\*\*\* Proteinuria with reactive deep stick in a random sample.

and standard deviations or as percentages for qualitative variables. Age difference between samples was analyzed by Student's t test. Association between qualitative variables was analyzed by contingency tables and Chi-squared. Crude and adjusted risk (odds ratio) for proteinuria and CRF associated to predictor variables was calculated with a conditional logistic regression model. A p value < 0.05 has been considered as statistically significant. All relevant differences are expressed with a 95% confidence interval.

## RESULTS

In the first phase, the following sample was obtained (table I): At coastline (Jaquilsco), 291 (35%) of the total 832 male inhabitants in 8 communities were studied. In the high zone (Sesorí), 62 (16%) of 388 males in three communities participated.

Mean age for the coastline sample (table I) was 50.2 ± 15.9 years, 85.9% were farmers, 80.4% had a history of pesticides exposure and 64.9% recognized frequent alcoholic beverages intake. One hundred people in this group were diagnosed with DM and/or AHT (34.36%), thus: 73 (25.1%) DM cases and 42 (14.4%) AHT cases, almost of all them without a previous diagnosis or control. Proteinuria was detected in 133 (45.7%) of the 291 studied men.

For the high zone group (table I), mean age was 54.8 ± 9.6 years, 91.9% were farmers, 85.5% had a history of pesticides exposure and 87.1% recognized frequent alcoholic beverages intake. Twenty pe-

ople in this group were diagnosed with DM and/or AHT (32.26%), thus: 5 (8.1%) DM cases and 16 (25.8%) AHT cases, almost of all them without a previous diagnosis or control. Proteinuria was detected in 8 (12.9%) of the 62 studied men.

When comparing both patient samples in Table I, we observed that there were no significant differences with respect to agricultural occupation or exposure to pesticides. High zone patients were 4.6 years (95%CI = 0.5-8.7 years) older than those at coastline. At coastline we found 32.8% (95%CI = 22.7-42.9%) more proteinuria cases than in the high zone (p < 0.0001). On the other hand, in the high zone there is 27.2% (12.2-32.2%) more alcoholism and a mild 11% (0.2-23%) increase in AHT frequency, whereas in the coastline zone there are 17% (8.6-25.4%) more DM cases.

The differences observed between cases that presented with proteinuria, as well as crude and adjusted risks associated with different predictive variables are shown in table II. Proteinuria was found in coastline zone males 32.8% more frequently (CI = 22.7-42.9%), as well as in those aged more than 60, those with elevated blood glucose levels or who were hypertensive. Exposure to neither pesticides nor alcoholic beverages consumption was associated to proteinuria presence. Agricultural occupation did not represent a higher risk either, although there was a tendency for a higher proteinuria percentage among farmers (84.4 vs. 90.4%).

In the conditional logistic regression model, predictable variables such as AHT, DM, region, age, agricultural occupation, exposure to pesticides and alcohol consumption were included. Variables asso-

**Table II.** Adult men with proteinuria in two zones of El Salvador: associated factors

	With proteinuria*	Odds Ratio		p
		Crude	Adjusted	
Total cases:	141 (100%)			
High-land zone** (n = 62):	8 (12.9%)			
Coastline zone*** (n = 291):	133 (45.7%)	5.68 (2.61 - 12.30)	8.04 (3.53 - 18.29)	< 0.0005
Younger than 40 years (n = 75):	14 (18.7%)			
40 to 60 years (n = 181):	76 (42.0%)	2.99 (1.55 - 5.78)	4.28 (2.04-9.01)	< 0.0005
Older than 60 years (n = 97):	51 (52.6%)	4.94 (2.48 - 9.86)	5.82 (2.64 - 12.84)	< 0.0005
Farmers (n = 307)	128 (90.8%)	1.82 (0.92 - 3.59)	1.62 (0.75 - 3.49)	0.056
Pesticides (n = 287):	113 (80.1%)	0.88 (0.51 - 1.56)	0.79 (0.42 - 1.47)	0.374
Alcoholism (n = 243):	97 (68.8%)	1.00 (0.63 - 1.58)	0.69 (0.39 - 1.22)	0.540
DM**** (n = 78):	48 (34.0%)	3.13 (1.86 - 5.27)	2.07 (1.18 - 3.63)	< 0.005
AHT**** (n = 58):	32 (31.2%)	2.1 (1.19 - 3.71)	2.25 (1.16 - 4.38)	0.008

\* Proteinuria with reactive deep stick in a random sample.

\*\* Rural communities of Sesori region, inland.

\*\*\* Rural communities of Jaquilisco region, at the Pacific Coast.

\*\*\*\* Provisional diagnoses.

ciated to the risk of presenting proteinuria were (Table II): AHT, DM, age and geographic zone, being the latter the one presenting the highest relative risk (OR). Age behaved as a confounding variable for proteinuria risk associated to the geographic area.

The small control sampling with deep sticks performed among some women in the coastline zone yielded one positive case (4%) out of 25 performed tests.

In the second phase, we could perform laboratory analyses in only 80 of 133 proteinuric coastline patients. Mean age for this group was  $55.1 \pm 12.5$  years, 87.5% were farmers, 82.5% had a history of pesticides exposure and 68.75% recognized frequent alcoholic beverages intake. A DM or AHT diagnosis was established in 36 (45%) of them. Average Hb was  $13.1 \pm 1.8$  g/dL, being less than 12 g/dL in 13 (16.25%) cases. Average serum creatinine was  $1.8 \pm 1.9$  mg/dL. CRF was diagnosed in 37 (46.3%) of these 80 proteinuric coastline patients studied in the second phase.

The mean age for this subgroup of 37 CRF people (table III) was  $57.5 \pm 11.8$  years, 89.2% were farmers, 83.8% had a history of previous exposure to pesticides and 70.3% recognized a frequent alcoholic beverages intake. Only one out of 37 males knew his diagnosis before hand and was medically controlled; the remaining 36 did not know having CRF. A DM and/or AHT diagnosis was established in 14 (37.8%), the remaining 23 (62.2%) did not present an important medical history or consumption of

nephrotoxic drugs or any other known risk factor that could explain their renal failure. For this CRF group, average creatinine was 1,5-3 mg/dL and only 2 (5.41%) patients had a creatinine greater than 4 mg/dL. Their average Hb was  $12.32 \pm 1.9$  g/dL, with only 9 cases with a Hb lower than 12 g/dL. With proteinuria stratification, it was observed that 30 (81.1%) had 15-30 mg/L, 5 (13.5%) had 100 mg/L, and only 2 (5.4%) 300 mg/L.

CRF in these patients was neither associated (Table III) to agricultural occupation, nor to pesticides, alcohol consumption, DM or AHT, probably due to the low number of included subjects and the important selection bias.

## DISCUSSION

With regards to the first phase of the present study, it can be observed that there exists a high proteinuria prevalence (45.7%) among men from studied communities at the Pacific Coast (table I). Within the limitation of the study simplicity and considering that diagnoses provided are provisional, it is worth mentioning that in almost two thirds of the cases proteinuria was isolated and the only symptom, that is not related to DM, AHT or other findings. When comparing coastline men characteristics with those of higher lands zones we observed a high degree of similarity in relation to the frequency of the studied variables (table I); however, the proteinuria presen-

**Table III.** Characteristics of 37 CRF men at the Pacific Coast of El Salvador

		P
Farmers:	33 (89.2%)	0.469
Exposure to pesticides:	31 (83.8%)	0.492
Usual alcoholism:	26 (70.3%)	0.489
Younger than 40 years:	2	
40 to 60 years:	18	
Older than 60 years:	17	
With previous diagnosis:	1 (2.7%)	
Without previous diagnosis:	36 (97.3%)	
Hemoglobin:	12.3 ± 1.9 g/dL	
Serum creatinine:	2.64 ± 2.5 mg/dL	
Proteinuria* 15 - 30 mg/dL:	30 (81.1%)	
Proteinuria* 100 mg/dL:	5 (13.5%)	
Proteinuria* 300 mg/dL:	2 (5.4%)	

\* Proteinuria with reactive deep stick in a random sample.

ce at the Jaquilisco coastal zone is very elevated and living in that region is an important risk factor for presenting it (OR = 8.04). The presence of proteinuria as a basic indicator of renal injury is significantly associated with the zone, even after adjusting for other confounders such as age, DM and AHT. The other studied characteristics, as working in agricultural labors, exposure to pesticides or locally distilled alcoholic beverages consumption, which could have, at least in theory, some effect on the appearance of renal injury in the zone, do not seem to be related to the presence or absence of proteinuria in the studied population.

In the second phase, and after the initial screening for proteinuria detection as a cheap and basic indicator of renal injury, we tried to look for CRF cases among coastline men that presented with proteinuria. Nevertheless, due to the lack of better resources and the limited access to Health Services, only 80 out of 133 men could have the basic laboratory analyses proposed. This loss of cases has represented an important limitation for the study objectives, however we have been able to demonstrate, by means of a modest and simple method, that the disease prevalence at the coastal zone is abnormally high since CRF was diagnosed in 37 out of 291 inhabitants initially studied, that is to say, at least 12.7% of the adult men of that zone are sick. Certainly, prevalence would have been even higher had it been possible to perform laboratory analyses to all 133 proteinuric men, or even better, to all the male population of the zone.

According to questionnaire results and in agreement with the profile encountered in the previous study<sup>1</sup>, most of them usually take locally produced alcoholic beverages of low quality, worked at cotton plantations two decades ago in the coastline zone, and have a frequent exposure to pesticides and weed killers. It has been speculated that such characteristics could play a role in the disease development<sup>1,3,7,8</sup> or be a way for exposure to other nephrotoxic agents<sup>9</sup>, however we perceive they are very frequent and usual conditions of both regions, independently of presence or absence of proteinuria and CRF, and we could not find any statistical association with any of them.

Almost all detected men with CRF were apparently «healthy», and only 14 out of 37 (34.8%) presented DM and/or AHT, diseases traditionally associated with CRF and that could be assumed, at an extreme, as its possible cause, but in the remaining 23 (62.2%) the etiology was unclear. This datum is also similar to the one observed at the hospital-based study<sup>1</sup>, where the cause could not be established in two thirds (66.8%) of the new reported cases. Again, the usual causes do not seem to explain such an elevated number of cases: there is something linked to the zone that will require more comprehensive studies in order to investigate environmental factors and occupational exposures to nephrotoxic agents such as ocratoxins<sup>10,11</sup> or heavy metals<sup>9,12</sup>, or little symptomatic variants of hereditary X-linked diseases such as Alport's<sup>13</sup> or Fabry's<sup>14</sup>. Although we acknowledge the limitations of the 37

CRF subjects analysis, its characteristics are of particular interest, highlighting that proteinuria is minimal (15 to 30 mg/dL) in 81.1% of cases, serum creatinine levels are moderately elevated ( $2.64 \pm 2.5$  mg/dL) and anemia is discreet (mean Hb  $12.32 \pm 1.9$  g/dL). It would seem that most of these men are at an early phase of a disease probably interstitial in its etiology, and therefore are still candidate to benefit from an adequate control and treatment to stop or slow down the progressive worsening of their renal function.

Curiously, although quantitative proteinuria values were not very elevated, their use as an initial screening method to minimize costs led to CRF diagnosis in 37 (27.8%) out of 133 patients selected in this way, showing that it may be a useful and economic method for detecting cases in that zone.

On the other hand, it is interesting to highlight that only one out of 37 CRF men was already diagnosed and under control, while the remaining 36 were unaware of their disease and most of them had never had access to a medical visit; it would seem that only the iceberg tip is currently visible to the National Health System. This is understandable should we consider that in that zone the Health System, optimizing its scant resources, focuses most of its efforts to looking after women and children, what constitutes a curious situation of an inverse gender discrimination. Moreover, only a few can access a third level care due to the limited accessibility and that familial economic support lies on the daily men work. In fact, in the hospital-based study<sup>1</sup> it could be observed that almost all of these CRF patients came in an emergency end-stage situation, requiring immediate dialysis onset at diagnosis. Finally, the National Health System Epidemiologic Registry does not include CRF as a notifiable entity, therefore it is not reported. After the study, all coastline men with proteinuria or a preliminary CRF diagnosis were referred to the second National Health System level, however none of them could receive an adequate nephrologic care or have access to dialysis programs, had they been necessary.

Finally, we must stress that unrevealed CRF prevalence in the zone is disproportionately high but easily detectable with low cost interventions using proteinuria as a basic indicator for renal injury. If cases are looked for, an early diagnosis can be made with simple and cheap methods. Broader and better sponsored studies should be undertaken to investigate the cause of this unusual CRF prevalence among farmers at the coast of El Salvador, and to investigate whether the situation is unique to the Country or it replicates along the Central American Pacific Coast. It would be highly desirable to perform fo-

llow-up epidemiologic studies in a large cohort of individuals, with a comprehensive data gathering and regulated laboratory studies that would include the determination of several toxicants such as heavy metals, ocratoxins, etc. It is necessary to keep on detecting unrevealed cases, but even more important is to offer those people the opportunity for receiving an appropriate care and replacement therapeutic options for their renal function, because each familial group depends on each one of these men and when they will progress to end-stage CRF a family will be left without economic support, and when they will die, each one of them will leave orphans and widows in this zone of the Pacific Coast of El Salvador.

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