María O. López-Oliva [a,*], Laura Álvarez [a],
Mª Luisa Testillano [b], Tamara Pérez [b],
María Fernández Nieto [a], Mª José Santana [a], Elena González [a],
Alicia Herrero [b], Rafael Selgas [a], Carlos Jiménez [a]

[a] *Nephrology Department, University Hospital La Paz, Madrid, Spain*
[b] *Pharmacy Department, University Hospital La Paz, Madrid, Spain*

* *Corresponding author.*
E-mail address: mlopezo@salud.madrid.org
(M.O. López-Oliva).

Non-critical urinary cadmium excretion as a risk factor associated with tubular markers of early kidney injury in Central Mexico

Niveles no-críticos de excreción urinaria de cadmio como factor de riesgo asociado con marcadores tubulares de daño renal temprano en la región central de México

Dear Editor:

Cadmium (Cd) is an ubiquitous element in nature and high levels of Cd exposure is considered a risk factor for renal injury; however, their nephrotoxic effects at low-environmental exposure levels are debated.[1,2]

Cd accumulates in the proximal tubule renal cells where inhibits the mitochondrial respiratory chain and this results in mitochondrial dysfunction and free radical formation.[3]

Some of the urinary markers used to evaluate Cd nephrotoxicity are N-acetyl-β-D-glucosaminidase (NAG), α1-microglobulin (α1M), β2-microglobulin (β2M) and the kidney injury molecule (KIM-1).[4] The aim of this study was to search for the effects of urinary cadmium excretion on markers of early renal injury in population living in suburban communities in central Mexico.

The study was done in 7 communities located close to Queretaro city in Central Mexico; farming and agricultural practices are common but these areas are rounded by manufacturing activities. We evaluated 90 voluntary healthy subjects ($\geq$20 years old), using a simple probabilistic sampling procedure on every of the communities studied. Those with current urinary tract infection, previous diagnosis of kidney disease, liver disease, cancer, or other chronic disease, as well as pregnant women were excluded.

A questionnaire was used to obtain information on personal health history, and risk factors to Cd exposure. Blood pressure measurements were obtained with an aneroid sphygmomanometer after a 5 min resting in sitting position, and blood samples were taken after a fasting $\geq$8 h during the same visit.

GFR was calculated with the CKD-Epi formula and spot urine samples for albumin, α1-microglobulin and cadmium analysis were collected in cadmium-free containers. Albumin and α1M were creatinine adjusted.

Cd measurements were done at the Department of Environmental Toxicology Laboratory (San Luis Potosi Medical School); and quantification was carried out with a Perkin-Elmer 3110 atomic absorption spectrometer.[5]

We categorized urinary Cd excretion in two groups according to CdU excretion and multivariate analysis was performed to identify risk factors for high Cd levels, albuminuria and higher urinary α1M. A *p* value $\leq$0.05 was considered as statistically significant and data were analyzed using the SPSS 23.0 software.

The overall analysis included 90 adults with no antecedent of occupational exposure to Cd, 66.6% of all participants were women and the mean age was 41 ± 12 years; CdU median levels were $0.37 \pm 0.41\,\mu g/gCr$ and few patients ($n = 3$) had CdU $\geq 1\,\mu g/gCr$.

Those subjects with CdU $\geq 0.37\,\mu g/gCr$ had higher levels of α1M (9.4 ± 9 vs $3.2 \pm 4\,\mu g/gCr$, $p = 0.001$) and albumin excretion (13.1 ± 24 vs $3.9 \pm 2.5\,g/gCr$, $p = 0.001$). Those patients with higher CdU excretion had a higher risk for α1M ≥ 10 (OR 5.0, CI95 1.4–18.6, $p = 0.01$) and micro-albuminuria (OR 20, CI95 1.0–39, $p = 0.04$).

In multivariate analysis, CdU was the most important risk factor associated with higher α1M excretion and albuminuria after adjustments for age, BMI, smoking status, blood pressure, lead concentration and GFR.

In non-smoking subjects, those with CdU $\geq 0.37\,\mu g/gCr$ had higher urinary excretion of α1M (7.5 ± 7.2 vs $3.3 \pm 4.7\,\mu g/gCr$, $p = 0.002$) and albumin (11.1 ± 18 vs $3.9 \pm 2.5\,g/gCr$, $p = 0.003$); CdU was associated with a higher risk for α1M $\geq 10\,\mu g/gCr$ (OR 4.1, CI95 1.1–19, $p = 0.03$), and CdU was the most important factor associated with higher α1M excretion.

Table 1 – Comparison of demographic and laboratory characteristics according to CdU excretion.

	Cd < 0.37 (µg/gCr) n = 64	Cd > 37 (µg/gCr) n = 26	p
Age (years)	40 ± 12	43 ± 14	NS
Females (%)	78	77	NS
Smokers (%)	12	27	0.04
BMI (kg/m²)	27.1 ± 4.6	28.8 ± 5.5	NS
SBP (mmHg)	112 ± 14	122 ± 20	0.003
DBP (mmHg)	74 ± 7	78 ± 8	0.007
α1M (µg/gCr)	3.2 ± 4.4	9.4 ± 9.8	0.000
AUE (g/gCr)	4 ± 2	13.1 ± 2.4	0.01
Pb	5.4 ± 2.7	6.6 ± 4.0	NS
Glucose (mg/dl)	92 ± 9.3	92 ± 9.8	NS
Urea (mg/dl)	28 ± 6.6	28 ± 8.8	NS
Creatinine (mg/dl)	0.86 ± 0.17	0.83 ± 0.18	NS
eGFR (ml/min)	82 ± 18	85 ± 23	NS
Uric acid (mg/dl)	4.3 ± 1.3	4.6 ± 1.7	NS

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; α1M: α1-microglobuline; AUE: albumin urinary excretion; GFR: glomerular filtration rate.

This is the first study done in Mexico to evaluate the effects of Cd on kidney injury markers such as albumin and α1M, and in this study we showed that in this population living in central Mexico the non-critical levels of urinary Cd excretion had an important effect on markers of tubular injury, though association with low GFR was not found.

Cadmium levels in this study were just above to those reported in other countries such as the United States (media 0.26 µg/gCr), Spain (media 0.28 µg/gCr), or Korea (media 0.30 µg/gCr)[6,7]; however, comparing the results with other studies that had shown nephrotoxicity associated to CdU, the threshold reported for CdU is higher (0.8–1.0 µg/gCr),[8,9] so our finding is of interest because the CdU levels analyzed in our study are in a range considered as non-nephrotoxic.

Tubular injury and urinary excretion of tubular injury markers are the first clinical manifestations of Cd nephrotoxicity, and some studies have found association between urinary α1M and tubular atrophy, GFR decline, and higher mortality; however its role in progressive kidney disease is controversial.[10]

Some limitations of this study are the small number of patients, the high representation of women, the lack of Cd environmental levels and of reliable epidemiological data about the prevalence of low GFR in the communities studied.

In conclusion, our study shows that non-critical Cd excretion is a risk factor associated with an increased excretion of markers of tubular injury and further work need to be done to test Cd as a possible toxin in the occurrence of CKD of unknown etiology in Mexico (Tables 1–2).

Conflict of interest

The authors declare that they do not have conflicting interest.

Acknowledgements

REFERENCES

1. Jarup L, Akesson A. Current status of cadmium as an environmental health problem. Toxicol Appl Pharmacol. 2009;238:201–8.
2. Wallin M, Sallsten G, Lundh T, Barregard L. Low-level cadmium exposure and effects on kidney function. Occup Environ Med. 2014;71:848–54.
3. Sabath E, Robles-Osorio ML. Renal health and the environment: heavy metal nephrotoxicity. Nefrologia. 2012;32:279–86.
4. Prozialeck WC, Edwards JR. Early biomarkers of cadmium exposure and nephrotoxicity. Biometals. 2010;23:793–809.
5. Trejo-Acevedo A, Diaz-Barriga F, Carrizales L, Domínguez G, Costilla R, Ize-Lema I, et al. Exposure assessment of persistent organic pollutants and metals in Mexican children. Chemosphere. 2009;74:974–80.
6. Ferraro PM, Costanzi S, Naticchia A, Sturniolo A, Gambaro G. Low level exposure to cadmium increases the risk of chronic kidney disease: analysis of the NHANES 1999–2006. BMC Public Health. 2010;10:304.
7. Lopez-Herranz A, Cutanda F, Esteban M, Pollán M, Calvo E, Pérez-Gómez B, et al. Cadmium levels in a representative sample of the Spanish adult population: the BIOAMBIENT.ES project. J Expo Sci Environ Epidemiol. 2016;26:471–80.
8. Jarup L, Hellstrom L, Alfven T, Carlsson M, Grubb A, Persson B, et al. Low level exposure to cadmium and early kidney damage: the OSCAR study. Occup Environ Med. 2000;57:668–72.
9. Byber K, Lison D, Verougstraete V, Dressel H, Hotz P. Cadmium or cadmium compounds and chronic kidney disease in workers and the general population: a systematic review. Crit Rev Toxicol. 2016;46:191–240.
10. Jotwani V, Scherzer R, Abraham A, Estrella MM, Bennett M, Cohen MH, et al. Association of urine alpha1-microglobulin with kidney function decline and mortality in HIV-infected women. Clin J Am Soc Nephrol. 2015;10:63–73.

Ma. Ludivina Robles-Osorio [a], Pablo García-Solís [a], Juan Carlos Solís-Sainz [a], Diana Montero-Perea [b], Itzel Avilés-Romo [b], Elizabeth Sabath-Silva [c], Angeles Ochoa-Martínez [d], Iván Pérez-Maldonado [d], Ernesto Sabath [a,e,*]

Table 2 – Multivariate analysis of variables associated with α1M and albumin urinary excretion.

	α1M			AUE	
	β	p		β	p
Age	−0.172	0.02	Age	−0.111	0.11
BMI	−0.059	0.42	BMI	0.065	0.36
GFR	−0.184	0.01	GFR	−0.091	0.19
Glucose	0.094	0.20	Glucose	−0.057	0.41
CdU	0.381	0.000	CdU	0.472	0.000

α1M: α1-microglobuline; AUE: albumin urinary excretion; BMI: body mass index; GFR: glomerular filtration rate.

[a] *Endocrinology and Metabolism Laboratory, Universidad Autónoma de Querétaro, Mexico*
[b] *Medical School, Universidad Autónoma de Querétaro, Mexico*
[c] *Cellular Biology and Physiology Department, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México, Mexico*
[d] *Department of Environmental Toxicology Laboratory, Medical School, Universidad Autónoma de San Luis Potosí, Mexico*
[e] *Renal Department, Hospital General de Querétaro, Mexico*

[*] *Corresponding author.*
E-mail address: esabath@yahoo.com (E. Sabath).

Inflammation in hemodialysis and their correlation with neutrophi-lymphocite ratio and platelet-lymphocyte ratio. [☆]

Inflamación en hemodiálisis y su correlación con los índices neutrófilos/linfocitos y plaquetas/linfocitos

Dear Editor,

Cardiovascular disease (CD), the leading cause of death in hemodialysis (HD) patients,[1] is closely related to inflammation. C-reactive protein (CRP) and interleukin-6 (IL-6) reflect inflammation and are associated with malnutrition and atherosclerosis.[2]

Platelets are fundamental for hemostasis and also have a role on inflammation and immunity[3] since they interact with the endothelium and cells of innate and acquired immunity.

During the last five years, the platelet/lymphocyte ratio (PLR) and the neutrophil/lymphocyte ratio (NLR)[4] have been proposed as potential markers of inflammation. The NLR is also related to systemic endothelial dysfunction.[5] Both PLR and NLR are easily obtained, however there is not much research relating PLR and NLR with inflammation in HD.

The objectives of the present study were: (1) To compare in 81 patients in HD with inflammation (PCR $\geq$10 mg/l) and 52 patients without inflammation (PCR $\leq$10 mg/l) the values of Hemoglobin (Hb), red cell distribution width (RDW), total lymphocyte count, total platelet count (TPC), mean platelet volume (MPV), PLR and NLR; (2) To analyze these parameters in patients with/without diabetes mellitus type 2 (DM2) and with/without inflammation; and (3) To determine the correlation between PLR and NLR with known biomarkers of inflammation and nutrition (PCR, IL-6, transferrin, ferritin and albumin).

The ethics and research committee approved the study. The study was performed at the Instituto Mexicano del Seguro Social in patients on HD for more that 3 months and between 18 and 79 years of age. The study was prospective, cross-sectional. Clinical history and laboratory tests were performed. Patients with infection or thrombocytopenia were excluded.

Statistical analysis was performed using the SPSS® v. 20 in Spanish. Depending on the data distribution comparisons were made using Student's *t* or *U* of Mann–Whitney, ANOVA or Kruskal–Wallis, Pearson or Spearman. Linear regression analysis was performed to identify independent factors associated to inflammation. We consider a statistically significant difference a $p < 0.05$.

A total of 133 patients were included, 51.1% male. The mean age was 45.86 ± 17.7 years, with a mean dialysis vintage of 45.4 ± 38.4 months; body mass index (BMI) 23.9 ± 5 Kt/V of 1.3 ± 0.09. Diabetes mellitus type 2 in 32% and hypertension in 78.9% of the patients. The main causes of end-stage renal disease were unknown (38.3%) and DM2 (32.3%).

The mean NLR was 3.5 (range: 0.28–61.8) and PLR 173.35 ± 98.5 (range: 40.2–778.9).

As compared with patients with PCR <10 mg/l, those with CRP >10 mg/l had increased levels of IL-6 (10.38 [range: 6.8–13.8 pg/ml] vs. 5.73 [range: 3.3–8.1 pg/ml]). The RDW were (15.9 ± 12.2 vs. $14.7 \pm 1.7.7\%$), total leukocytes (6.31 ± 1.75 vs. $5.38 \pm 1.56 \times 10^3/\mu l$), PLR ($189.8 \pm 114.4$ vs. 149 ± 61, $p < 0.05$), NLR (3.53 (range: 0.3–28) vs. 2.41 (range: 0.28–7.58), $p = 0.005$), total number of neutrophils (4.0 ± 1.4 vs. $3.1 \pm 1.36 \times 10^3/\mu l$, $p = 0.001$).

The number of lymphocytes and Hb level were comparatively lower in the group with inflammation 1.48 ± 0.77 vs. $1.62 \pm 0.93 \times 10^3/\mu l$ ($p = 0.52$) and 9.7 ± 2.2 vs.10.3 ± 2 g/L ($p = 0.17$), respectively. The MPV and number of platelets were not significantly different between the two groups.