

## In Focus

# The MesoAmerican nephropathy: a regional epidemic of chronic kidney disease?

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In the history of humanity, the struggle for survival has been an ongoing issue as human beings face epidemics from different sources, environmental adversities and exposure to toxins.

The kidneys receive approximately one fifth of blood volume per unit time and, given their secretory and excretory functions, they are commonly victimized by environmental toxins or drugs ingested for therapeutic or recreational reasons. In recent years, there has been a substantial rise in kidney diseases caused by drugs, such as heroin, cocaine and amphetamines, and a surge in kidney diseases induced by medications (non-steroidal anti-inflammatory agents, antibiotics, lithium, platinum, immunosuppressive agents, to mention a few) or diagnostic agents (such as, contrast agents).

On occasion, epidemic or endemic forms of kidney diseases caused by environmental toxins have been described. A typical example is the so-called Balkan nephropathy. This is an endemic form of tubule-interstitial nephropathy identified among persons living in rural areas of the Danube River in Serbia, Bulgaria, Croatia, Romania and Bosnia [1]. After approximately 50 years of epidemiologic and clinical studies, it was determined that aristolochic acid, a contaminant of the wheat flour, was the likely cause of this nephropathy. This toxin is also the cause of Chinese herb nephropathy, first described in a cluster of cases in Belgium. Chronic kidney disease (CKD) caused by aristolochic acid has been described in multiple regions of the world, particularly in Asia, in association with ingestion of contaminated food products, beverages and herbal remedies containing aristolochic acid [2].

More recently, several epidemiological studies have described an excess of CKD among younger adult males in the geographic region that includes Southeastern Mexico, Guatemala, Belize, El Salvador, Honduras, Nicaragua, Costa Rica and Panama. This condition is now known as Mesoamerican Nephropathy (MeN).

This form of CKD affects primarily young male agricultural workers, exposed to very hot conditions especially in the sugarcane fields. Clinically, they usually present with normal or mildly elevated blood pressure, reduction in estimated glomerular filtration rate (eGFR), non-nephrotic proteinuria, hyperuricemia and hypokalemia. Kidney biopsies show a chronic tubulointerstitial disease with associated glomerulosclerosis [3].

A large population-based cross-sectional study involving approximately 3000 individuals was conducted by Lebov *et al.* [4] in León, Nicaragua, to evaluate the association between previously investigated risk factors and CKD. CKD prevalence was 13.8% for males and 5.8% for females. Male gender, older age, living in a rural zone, lower education level, self-reported high blood pressure, more years of agricultural work and *lija* (unregulated alcohol) consumption, were significantly associated with CKD.

In another study, dialysis enrollment rates were evaluated in the The National Center for Chronic Kidney Disease Treatment (Unidad Nacional de Atención al Enfermo Renal Crónico), the largest provider of dialysis in Guatemala. The incidence of CKD appeared to be higher in the high temperature and sugar cane growing regions [5].

Laws *et al.* [6] measured urine albumin, serum creatinine and eGFR among 284 Nicaraguan sugarcane workers performing seven distinct tasks. eGFR varied by job and decreased during the harvest in seed cutters ( $-8.6$  mL/min/1.73 m<sup>2</sup>), irrigators ( $-7.4$  mL/min/1.73 m<sup>2</sup>) and cane cutters ( $-5.0$  mL/min/1.73 m<sup>2</sup>), as compared with factory workers. The number of years employed at the company was negatively associated with eGFR. Fewer than 5% of workers had albumin-to-creatinine ratio (ACR) >30 mg/g. This study concluded that the decline in kidney function during the harvest and the differences by job category and employment duration provide evidence that one or more risk factors of CKD are occupational.

In this issue of *NDT*, Ramírez-Rubio *et al.* [7] evaluated whether a greater prevalence of kidney damage might be present even in Nicaraguan children. To this end, they collected a questionnaire and a urine sample in 200 adolescents aged 12–18 years with no prior work history and selected from four different schools in Nicaragua, to establish potential associations between CKD and risk factors known to be present in adults with this disease. These investigators measured several urinary markers of kidney damage, including: urine albumin excretion, neutrophil gelatinase-associated lipocalin (NGAL) as a marker of distal renal tubule injury, N-acetyl-D-glucosaminidase (NAG) as a marker of proximal tubular epithelial cells injury, and interleukin 18, a marker of tubular inflammation and necrosis.

Proteinuria was detected in 3.5% and glucosuria in 1% of participants and did not differ by school. The urine concentration of NGAL and NAG was higher in those schools and regions within Nicaragua with increased CKD risk. Although interpretation of these urine biomarkers is limited because of the lack of population reference values, the results of this study suggest the possibility of early kidney damage in adolescents from this region, prior to occupational exposures.

The causes of this disease remain unknown, but recurrent dehydration, unregulated alcohol (lija) and exposure to agricultural products have been suggested as potential causes [8].

The First International Research Workshop on MeN met in Costa Rica in November 2012 to discuss how to establish the extent and degree of MeN, examine relevant causal hypotheses, and to focus efforts to control or eliminate the disease burden. This workshop established that the cause of MeN remains uncertain; however, the group suggested that repeated episodes of occupational heat stress and water and solute loss, in combination with exposure to other nephrotoxic medication, or exposure to inorganic arsenic, leptospirosis or pesticides, might be responsible for this epidemic [9].

Central America has a long-standing history of misuse of agrochemical products [10], and some pesticides commonly used in this region are clearly nephrotoxic and may be responsible for the MeN [11–13].

More studies are urgently needed to establish the causes of MeN and role of pesticides in this epidemic to implement public health interventions that might put an end to this epidemic in Central America.

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

- Grollman AP, Shibutani S, Moriya M *et al.* Aristolochic acid and the etiology of endemic (Balkan) nephropathy. *Proc Natl Acad Sci USA* 2007; 104: 12129–12134
- Debelle FD, Vanherweghem JL, Nortier JL. Aristolochic acid nephropathy: a worldwide problem. *Kidney Int* 2008; 74: 158–169
- Correa-Rotter R, Wesseling C, Johnson RJ. CKD of unknown origin in Central America: the case for a Mesoamerican nephropathy. *Am J Kidney Dis* 2014; 63: 506–520
- Lebov JF, Valladares E, Peña R *et al.* A population-based study of prevalence and risk factors of chronic kidney disease in León, Nicaragua. *Can J Kidney Health Dis* 2015; 2: 6
- Laux TS, Barnoya J, Guerrero DR *et al.* Dialysis enrollment patterns in Guatemala: evidence of the chronic kidney disease of non-traditional causes epidemic in Mesoamerica. *BMC Nephrol* 2015; 16: 54
- Laws RL, Brooks DR, Amador JJ *et al.* Changes in kidney function among Nicaraguan sugarcane workers. *Int J Occup Environ Health* 2015; 21: 241–250
- Ramírez-Rubio O, Amador JJ, Kaufman JS *et al.* Urine biomarkers of kidney injury among adolescents in Nicaragua, a region affected by an epidemic of chronic kidney disease of unknown etiology. *Nephrol Dial Transplant* 2015; doi: 10.1093/ndt/gfv292
- Robey RB. Cyclical dehydration-induced renal injury and Mesoamerican nephropathy: as sweet by any other name? *Kidney Int* 2014; 86: 226–229
- Wesseling C, Crowe J, Hogstedt C *et al.* Resolving the enigma of the mesoamerican nephropathy: a research workshop summary. *Am J Kidney Dis* 2014; 63: 396–404
- Aragon A, Aragón C, Thörn Å. Pests, peasants, and pesticides on the northern Nicaraguan Pacific plain. *Int J Occup Environ Health* 2001; 7: 295–302
- Bhupindervir Kaur B, Khera A, Sandhir R. Attenuation of cellular antioxidant defense mechanisms in kidney of rats intoxicated with carbofuran. *J Biochem Mol Toxicol* 2012; 26: 393–398
- Li Q, Peng X, Yang H *et al.* Deficiency of multidrug and toxin extrusion 1 enhances renal accumulation of paraquat and deteriorates kidney injury in mice. *Mol Pharm* 2011; 8: 2476–2483
- Siddharth M, Datta SK, Bansal S *et al.* Study on organochlorine pesticide levels in chronic kidney disease patients: association with estimated glomerular filtration rate and oxidative stress. *J Biochem Mol Toxicol* 2012; 26: 241–247

Received for publication: 23.11.2015; Accepted in revised form: 24.11.2015