AJKD

Perspective

Heat Stress Nephropathy From Exercise-Induced Uric Acid Crystalluria: A Perspective on Mesoamerican Nephropathy

Carlos Roncal-Jimenez, BS,[1,*] Ramón García-Trabanino, MD,[2,*] Lars Barregard, MD,[3] Miguel A. Lanaspa, PhD,[1] Catharina Wesseling, MD, PhD,[4] Tamara Harra, BS,[1] Aurora Aragón, MD, PhD,[5] Felix Grases, MD,[6] Emmanuel R. Jarquin, MD,[7] Marvin A. González, MD,[5,8] Ilana Weiss, MPH, MA,[9] Jason Glaser, BA,[9] Laura G. Sánchez-Lozada, PhD,[10] and Richard J. Johnson, MD[1,11]

Mesoamerican nephropathy (MeN), an epidemic in Central America, is a chronic kidney disease of unknown cause. In this article, we argue that MeN may be a uric acid disorder. Individuals at risk for developing the disease are primarily male workers exposed to heat stress and physical exertion that predisposes to recurrent water and volume depletion, often accompanied by urinary concentration and acidification. Uric acid is generated during heat stress, in part consequent to nucleotide release from muscles. We hypothesize that working in the sugarcane fields may result in cyclic uricosuria in which uric acid concentrations exceed solubility, leading to the formation of dihydrate urate crystals and local injury. Consistent with this hypothesis, we present pilot data documenting the common presence of urate crystals in the urine of sugarcane workers from El Salvador. High end-of-workday urinary uric acid concentrations were common in a pilot study, particularly if urine pH was corrected to 7. Hyperuricemia may induce glomerular hypertension, whereas the increased urinary uric acid may directly injure renal tubules. Thus, MeN may result from exercise and heat stress associated with dehydration-induced hyperuricemia and uricosuria. Increased hydration with water and salt, urinary alkalinization, reduction in sugary beverage intake, and inhibitors of uric acid synthesis should be tested for disease prevention.

Am J Kidney Dis. 67(1):20-30. © *2016 by the National Kidney Foundation, Inc.*

INDEX WORDS: Mesoamerican nephropathy (MeN); heat stress nephropathy; uric acid crystalluria; etiology; chronic kidney disease (CKD); rhabdomyolysis; uric acid disorder; uricosuria; hyperuricemia; urinary acidification; sugarcane workers; physical exertion; dehydration; Central America; tubular injury; hypothesis.

An epidemic of chronic kidney disease (CKD) of unknown cause is occurring along the Pacific coast of Central America. Although it was first described in 2002,[1] the disease has likely been present for decades.[2] The epidemic, known as Mesoamerican nephropathy (MeN), is observed primarily in men who are working manually in the sugarcane fields in the hotter lower altitudes along the Pacific coast.[3,4] However, MeN also has been reported among farmers of other crops (eg, cotton, corn, and beans), miners, and fishermen, as well as construction, port, and transportation workers living in the same region.[5-8] Individuals typically are asymptomatic,[9] but have an elevated serum creatinine level with absent or minimal proteinuria.[10] Kidney biopsy, when performed, reveals chronic tubulointerstitial disease, often with glomerulosclerosis and evidence of kidney ischemia.[11] Progression to end-stage renal disease is common, and mortality is high due to the scarcity of dialysis therapy. An estimated 20,000 people have died from the epidemic.[12] A variety of potential causes have been proposed, including exposure to

From the [1]Division of Kidney Diseases and Hypertension, University of Colorado, Denver, CO; [2]Scientific Board, Department of Investigation, Hospital Nacional Rosales, San Salvador, El Salvador; [3]Occupational and Environmental Medicine, Sahlgrenska University Hospital and University of Gothenburg, Gothenburg, Sweden; [4]Unit of Occupational Medicine, Institute of Environmental Medicine (IMM), Karolinska Institutet, Stockholm, Sweden; [5]Research Center on Health, Work and Environment (CISTA), National Autonomous University of Nicaragua at León (UNAN-León), León, Nicaragua; [6]University of Balearic Islands, Palma de Mallorca, Spain; [7]Agencia para el Desarrollo y la Salud Agropecuaria, San Salvador, El Salvador; [8]Department of Non-communicable Disease Epidemiology of London School of Hygiene and Tropical Medicine, London, United Kingdom; [9]La Isla Foundation, San Salvador, El Salvador; [10]Laboratory of Renal Physiopathology and Nephrology Department, INC Ignacio Chavez, Mexico City, Mexico; and [11]Division of Nephrology, Eastern Colorado Health Care System, Department of Veteran Affairs, Denver, CO.

[*]C.R.-J. and R.G.-T. contributed equally to this work.

Received April 26, 2015. Accepted in revised form August 7, 2015. Originally published online October 5, 2015.

Address correspondence to Richard J. Johnson, MD, Division of Renal Diseases and Hypertension, University of Colorado Denver, 12700 E 19th Ave, Rm 7015, Aurora, CO 80045. E-mail: richard.johnson@ucdenver.edu

0272-6386

http://dx.doi.org/10.1053/j.ajkd.2015.08.021

nephrotoxic pesticides and agrochemicals, use of nonsteroidal anti-inflammatory agents, heavy metal exposure, leptospirosis, and chronic recurrent dehydration (the most favored hypothesis).[3,4]

Could MeN Be a Uric Acid Disorder?

In 1974, Knochel et al[13] suggested that hyperuricemia and uricosuria might have an etiologic role in the condition of "heat stress" nephropathy. Serum uric acid levels commonly increase after exercise in hot conditions, such as from marathon running and off-road motocross, often in association with acute kidney injury (AKI).[14-17] Despite such studies, the pathologic mechanism has not been further explored. Here, we revisit the hypothesis that hyperuricemia and cyclical uricosuria associated with volume depletion (salt loss) and dehydration (water loss)[18] have a contributory causal role in MeN. Specifically, we hypothesize that MeN is initiated by the combination of heat, exercise, and recurrent dehydration (Fig 1).

Daily Dehydration and Volume Depletion

People who work in sugarcane fields are exposed to significant heat that tends to exceed recommended work practices made by the US Occupational Safety and Health Administration.[19,20] Although some sugarcane workers drink as much as 1 to 2 L per hour while they work, they have been shown to develop a modest elevation in serum osmolarity during the day, as well as reduced urine volumes with elevated urinary osmolarity and high urine specific gravity consistent with a water-depleted state.[21,22] While it is likely that workers experience both sodium and water loss, the latter predominates because sweat is hypotonic. Thus, individuals working in the sugarcane fields develop signs of dehydration on a daily basis.

Subclinical Rhabdomyolysis

Exercise in the heat can result in mild muscle injury together with an increase in blood levels of creatine kinase—features consistent with subclinical rhabdomyolysis—in association with biomarkers of kidney damage and decreased kidney function.[14,16,23] The heat component has been shown to be an important factor in increasing the susceptibility to rhabdomyolysis.[23] Intense exercise in the heat of sugarcane fields has been reported to result in mild muscle injury, with a doubling of creatine kinase level.[24] Thus, individuals working in sugarcane fields are at increased risk for muscle injury that is not uncommonly associated with subclinical rhabdomyolysis.

Hyperuricemia

Although subclinical rhabdomyolysis is thought to carry relatively minimal risk for the development of decreased kidney function, it releases substrate (nucleic acids) from the damaged muscle that could

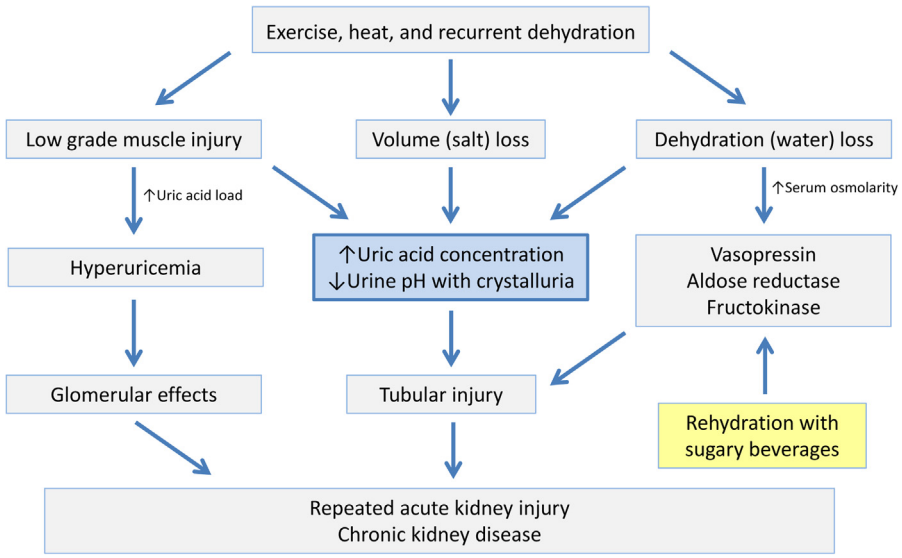

Figure 1. Proposed mechanism for Mesoamerican nephropathy. Exercising under hot conditions with inadequate hydration results in both dehydration (water loss), with an increase in serum osmolarity, and salt loss (volume depletion). An increase in serum uric acid levels occurs from subclinical muscle injury (increased substrate release) and water and salt depletion (increased reabsorption). Volume depletion concentrates the urine, while acid load (ie, lactate) and the effects of aldosterone on the kidney acidify it. As the workday proceeds, uric acid concentrations exceed their solubility due to both high concentrations and urine acidity. Serum uric acid results in glomerular hypertension, while urinary uric acid injures tubules through crystalline and noncrystalline effects. Low-grade proximal tubular injury also occurs from an osmolarity-induced increase in circulating vasopressin and activation of aldose reductase and fructokinase in the proximal tubule, the latter of which may be amplified by drinking fructose-containing soft drinks or other sugary beverages. Kidney injury occurs and is amplified on a daily basis with recurrent exposure to heat, exercise, and dehydration. Over time, chronic kidney disease develops.