Chronic Kidney Disease of Unknown Etiology: A Disease Related to Global Warming?

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Chronic kidney disease (CKD) is increasingly common throughout the world, largely due to the burgeoning epidemics of obesity and diabetes. Not only are diabetic nephropathy and hypertension the two most common causes of end-stage renal disease, but persons with obesity and metabolic syndrome also frequently show early signs of kidney disease well before diabetes and high blood pressure become apparent. Thus, a major focus has been on identifying the underlying mechanisms by which obesity and insulin resistance might predispose to kidney damage.

While obesity and diabetes represent the "big behemoth" in the room, there are areas of the world where CKD is rocketing yet these conditions are almost absent. In Central America, for example, an epidemic of CKD is striking agricultural communities from Guatemala to Panama, with some of the hardest hit areas being in Pacific coastal communities in Nicaragua and El Salvador.

A similar outbreak of CKD is occurring among workers in the rice paddies of northern Sri Lanka. These patients typically are not obese, do not have diabetes and have normal or only mildly elevated blood pressure. They do not show evidence of glomerular disease, as they are non-nephrotic and usually have no blood cells or cell casts in the urine sediment. Renal biopsies usually show extensive kidney scarring, primarily tubulointerstitial, and secondary glomerulosclerosis and glomerular ischemia.[1] Because these patients do not appear to have any of the common causes of CKD, their disease is often described as being *of unknown etiology*, or labeled for the region they live in, as in *Mesoamerican nephropathy*.

A major effort is now under way to identify the cause of these mysterious diseases. Important discoveries related to past local CKD epidemics have stimulated interest in the possible role of toxins such as agrochemicals, pesticides, silica, or heavy metals in the current epidemics. For example, *Aristolochia* is now recognized as the etiologic agent for Balkan nephropathy and for Chinese herbs nephropathy. Cadmium contamination of the Jinzu River in Japan in the early 1900s was identified as the cause of the outbreak of itai-itai disease, associated with CKD, proximal tubular injury and hypophosphatemic rickets.

While it seems likely that toxins may be involved, our group has focused on another potential driver, which we believe is underappreciated but may play an active role, not only in these emerging epidemics, but also "under the radar" in CKD generally throughout the world. Specifically, there is increasing evidence that recurrent dehydration may lead to kidney damage. Evidence for such a mechanism was recently shown in mice, in which recurrent dehydration resulted in mild tubulointerstitial injury with fibrosis.[2]

More recently, work from the Sánchez-Lozada laboratory has also shown that even subtle recurrent dehydration can result in oxidative stress in the kidney and low-grade tubular and glomerular injury (Sánchez-Lozada LG, personal communication). The mechanism of injury appears to be the consequence of recurrent increases in serum osmolarity that trigger release of vasopressin and activation of the polyol pathway in the kidney. Vasopressin may induce renal injury due to its hemodynamic effects as well as its ability to cause oxidative stress to the mitochondria.[3] Activation of aldose reductase in the polyol pathway leads to local generation of fructose, which then is metabolized by fructokinase in the proximal tubule, resulting in local oxidative stress and inflammation.[2] Interestingly, rehydration with soft drinks appears to exacerbate renal injury in this model, likely by providing fructose substrate that can feed these pathways (Sánchez-Lozada LG, personal communication).

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In Central America, the group with highest CKD risk appears to be sugarcane workers, and the most reliable occupational data have come from this group. Their working conditions are extreme; in one of the most affected regions, Nicaragua's Chinandega Department, temperatures during the sugarcane harvest's most intense period average highs of 93 °F (33.9 °C).

Labor rights studies and epidemiological research have shown that workers have an average fluid loss of 2.4 kg a day and may be subject to workdays of up to 12 hours, with some workers having inadequate access to water, rest or shade. Rehydration drinks, either provided to workers or brought to the fields by them, are also often high in sugar, and some workers also chew sugarcane during the workday, ingesting more sugar as a means of providing quick energy. Workers have also reported heat exhaustion during the harvest season.[4]

The world is progressively warming, and workers involved in heavy labor in hotter climates are being exposed to high temperatures where dehydration is increasingly likely. Labor practices do not always allow for sufficient rehydration breaks. At the same time, a dramatic rise in intake of sugary beverages has occurred over the last decades, and while there has been a leveling off in the USA over the last few years, these still represent one third of added sugar intake in the country.

We believe that the combination of recurrent dehydration, coupled with inadequate hydration, or with hydration with sugary solutions, is likely an unrecognized major contributor to the CKD epidemics. Furthermore, dehydration also predisposes to urinary concentration, increasing potential for concentrating environmental toxins.

It is important to continue to investigate toxins, heavy metals and other potential ways to explain the CKD epidemics that are emerging throughout the world. However, it seems likely that global warming and inadequate hydration practices are also major factors. Attention must also be directed to labor practices enforced by companies that may impair the ability of

workers to stay hydrated. We propose intervention trials aimed at improving working conditions, including increased number of breaks with access to shade, provision of adequate hydration, and encouraging consumption of fluids that do not contain large amounts (>20 g per serving) of sugar or high fructose corn syrup. There is an encouraging precedent for improving work practices in the United States' OSHA Heat Illness Prevention Campaign (Water.Rest.Shade). This proposes water intake every 15 minutes in hot conditions, which we believe provides the basis for an evaluable intervention to protect sugarcane workers and other at-risk groups in the affected regions. If results of these trials are positive, they may also provide a stimulus to determine if subtle dehydration and/or hydration with sugary solutions may also be risk factors for CKD in the general population, including subjects with obesity and/or metabolic syndrome.

1. Wijkstrom J, Leiva R, Elinder CG, Leiva S, Trujillo Z, Trujillo L, et al. Clinical and pathological characterization of mesoamerican nephropathy: a new kidney disease in Central America. Am J Kidney Dis. 2013;62:908–18.
2. Roncal CA, Ishimoto T, Lanaspa MA, Rivard CJ, Nakagawa T, Ejaz AA, et al. Fructokinase activity mediates dehydration-induced renal injury. Kidney Int 2013 Dec 11:1–9. DOI: 10.1038/ki.2013.492. [Epub ahead of print]
3. Bankir L, Bouby N, Ritz E. Vasopressin: a novel target for the prevention and retardation of kidney disease? Nat Rev Nephrol. 2013;9:223–39.
4. Hutchinson Y, Glaser J. Sickly Sweet: Human Rights Conditions for Sugarcane Workers in Western Nicaragua. La Isla Foundation 2014.

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