

Editorial

Chronic Kidney Disease Epidemic and the Developing World

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In the past century, several epidemics of Chronic Kidney Disease (CKD) occurred around the World, which challenged the medical and scientific community to find the cause and the cure. At least two were eventually traced to exposure to nephrotoxic substances. In the late 1920s an epidemic of “nephritis” in Queensland, Australia was linked to the exposure to lead during childhood. Lead, leaching from paint on railings of verandas of wooden houses was chronically ingested by children [1]. Starting in the early 1960s, the occurrence of the so-called Balkan Endemic Nephropathy (BEN) challenged the Medical establishment to search for a cause, which remained elusive for nearly 50 years. BEN was eventually attributed to contamination of wheat grains and flour by *Aristolochia clematitis*, which contains aristolochic acid, a potent nephrotoxin [2]. Aristolochic acid was also identified as the cause of Chinese Herb Nephropathy, another form of CKD that was first reported in young women from Belgium, consuming herbal supplements for weight loss. The supplements were found to be contaminated with *Aristolochia fanchi*. Both conditions progress to end-stage renal disease and are also associated with increased risk of bladder cancer [3]. Therefore, the more inclusive term, “aristolochic acid nephropathy” has been proposed.

In the past 10 years, two seemingly disparate regions of the world, namely the North Central region of Sri Lanka and the coastal regions of several Central American countries (Guatemala, El Salvador, Nicaragua, and Costa Rica) have witnessed an alarmingly high prevalence of CKD, primarily afflicting young men working in Chena cultivation or in sugar cane plantations, respectively. The affected individuals do not have the traditional risk factors for CKD, such as diabetes or hypertension. They remain asymptomatic but show progressive decline in GFR, low grade non-nephrotic proteinuria, hyperuricemia and hypokalemia. Because no cause has been found, the condition has been termed “CKD of unknown etiology” or CKDu. In recent years, several studies have been undertaken in an attempt to determine the cause or causes of CKDu. A number of theories have emerged, some of which have been tested with additional studies in Sri Lanka and Central America. In Sri Lanka, high concentrations of cadmium and arsenic were found in the soil and in the urine of individuals with CKDu [4]. Furthermore, the

wide use of agrochemicals in this region has led to the hypothesis that glyphosate, a common pesticide used on crops, combined with the presence of hard water, could chelate nephrotoxic metals such as cadmium and arsenic, increasing their concentrations in drinking water [5]. Increased levels of heavy metals have not been shown in Central America to the extent seen in Sri Lanka, so this mechanism cannot explain CKDu seen outside of Sri Lanka. Another plausible theory is that heat stress with recurrent dehydration along with the frequent use of non-steroidal anti-inflammatory drugs and possible exposure to environmental toxins or infections such as leptospirosis, may result in kidney injury [6].

Between 2009 and 2012, a series of epidemiologic studies were conducted in Nicaragua by Daniel Brooks and colleagues from Boston University. They concluded that chronic volume depletion and muscle damage along with environmental exposure to agrochemicals are plausible hypotheses for the very high prevalence of CKDu in León and Chinandega departments in Nicaragua [7]. Scientific inquiry into the mechanisms of kidney injury in these regions is also advancing. Richard Johnson and colleagues at the University of Colorado have shown that dehydration leads to activation of polyol pathway, resulting in increased conversion of glucose to sorbitol and fructose, which are metabolized by the endogenous fructokinase to uric acid, oxidants and chemokines [8]. In support of this hypothesis, they recently showed that fructokinase-deficient mice are protected from kidney damage, following recurrent, heat-induced dehydration [9]. Despite its attractiveness, many experts believe that other factors are also involved in CKDu and should be explored. Increased awareness has resulted in increased funding and several new research projects are currently underway.

In November 2012, the Program for Work, Environment and Health in Central America (SALTRA) convened a workshop in San José, Costa Rica to address the issues related to CKDu, which they named “Mesoamerican Nephropathy”. The objectives of this research workshop were to: (1) describe the state of the art of the Mesoamerican CKDu, including clinical, environmental and social aspects; (2) identify gaps in knowledge and propose specific and effective preventive and mitigation measures; (3) prioritize a research agenda and identify methods to obtain the needed knowledge; (4) facilitate and promote collaboration between different research groups and institutions, and use scarce resources more effectively, (5) provide a platform for raising international awareness and increase research funding [9]. Considering that CKDu primarily affects people living in rural areas of countries with limited healthcare resources, many affected individuals die of end-stage renal disease, due to lack of access to renal replacement therapy or transplantation. So, primary prevention may be the best solution for these impoverished workers. A recent publication of biopsy findings in 8 patients from El Salvador has provided the histological characteristics of Mesoamerican Nephropathy. Kidney sections showed extensive glomerulosclerosis,

signs of chronic glomerular ischemia, tubular atrophy, interstitial fibrosis but only mild vascular lesions [10].

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