CKD of Unknown Etiology: Is Taiwan Another Hotspot?

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Kidney Int Rep (2024) **9**, 4–6; https://doi.org/10.1016/j.ekir.2023.11.014

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Chronic kidney disease (CKD) is fast becoming a global health problem forecasted to reach epidemic proportions over the next few decades.[1] In 2022, it was reported to affect >10% of the world's population or approximately 840 million individuals.[2] Although diabetes, hypertension, smoking, and obesity are well-known risk factors; causes of CKD in developing countries are not as well delineated. According to the most recent survey in India, above 70% of patients with CKD could be defined as CKD of unknown etiology (CKDu).[3] The first formal mention of a possible new pathogenic entity for CKD and ESKD was published in 2002 by Trabanino *et al.*,[4] who also reported that over 70% of the population with advanced CKD in El Salvador had a disease of unknown origin. Since 2006, international workshops under SALTRA, a program on Health and Work in Central America, began to recognize an abnormal prevalence of CKDu in Central America. It was characterized as a progressive decline in GFR of otherwise asymptomatic individuals, predominantly men, aged 20 to 60 years, working mostly in sugarcane and cotton plantations along the coasts of El Salvador and Nicaragua. At the time, it was termed Mesoamerican Nephropathy.[5] In the 1990s, similar epidemics were reported in the North-Central province of Sri Lanka (Sri Lankan nephropathy), Andhra Pradesh of India (Uddanam nephropathy), and in countries such as Egypt and Tunisia.[6] Although the majority of the studies are centered in Central America, it is yet to be known if the reports from other parts of the world are the same disease condition.

In a recent issue of *Kidney International Reports*, Chang *et al.*[7] utilized a nationwide screening database combined with claims data and temperature data to explore the impact of farming occupation and ambient temperature on risks of CKD through a nested case-control study. They identified that the farming occupation, compared to other professions, had a 9% increased risk for CKDu (odds ratio = 1.09, 95% confidence interval = 1.001–1.18) but not for CKD. In addition, single lag time (8, 9, 10, 11, and 12 months) average environmental temperature is both associated with increased likelihood of CKD and CKDu, and cumulative lag (0–12 months) temperature effect is only associated with increased likelihood of CKD but not CKDu.[7] The results are intriguing and should encourage more future research to explore mechanisms of the long-term impacts of temperature on kidney health.

The proportion of high ambient temperature extremes in Taiwan has dramatically increased in summer. It will increase even more in the future.[8] More cases of kidney damage caused by extreme ambient temperature environments are expected to be seen in outpatient visits or emergency departments. However, there have been few opportunities to meet those patients recently. Therefore, we propose a useful theoretical concept for future preventive and care actions for heat-inducing kidney disease (Figure 1). People may usually work in a heated environment based on their previous weather exposure experiences. They are unaware of their aging, illness, specific drug use (e.g., diuretics), and rapid change of extreme ambient temperature in one work field. Three possible consequences may be expected: severe enough to cause ESKD and death in one work field, mildly symptomatic and are referred to clinical care, or asymptomatic and undetected. As physicians, we more commonly see patients who fall under the second scenario with repeated or nonrepeated acute kidney injuries, possible transfer to acute kidney disease (<3 months), and finally, CKD. The final scenario may occur

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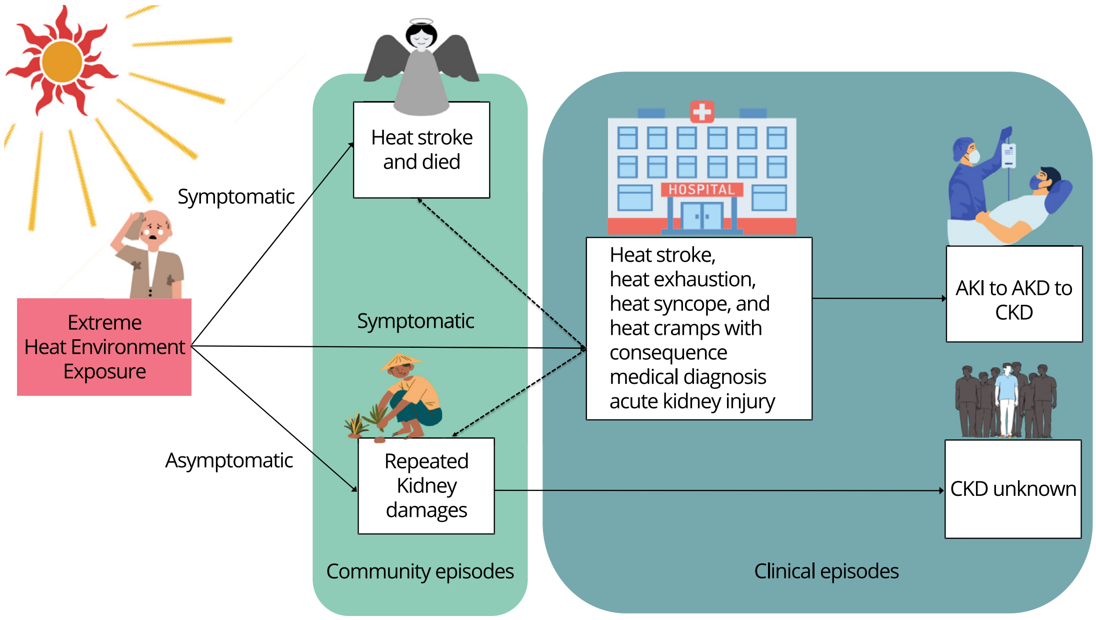

Figure 1. Hypothetical scenarios for kidney damages caused by heat environment exposure. Solid line: ideal care flow; dashed line: latent flow. AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease.

among those who experience repeated asymptomatic injuries from heat weather over several months or years; however, screening and diagnosis with CKD were unknown by the care system.

The study of CKDu remains to be a challenge. The current definition loosely excludes only traditional causes of CKD such as diabetes and hypertension, leaving inconsistencies in the exclusion of other potential causes of "normotensive and nondiabetic CKD". How do we accurately distinguish one from the other? Existing evidence of CKDu from different parts of the world also report different risk factors, leaving no universally accepted pathogenic hypothesis for this disease. Studies done in different settings add to a growing list of potential causes: environmental toxins, pesticides, arsenic and other heavy metals, hard water, and infectious diseases to name a few.[9] Most authors will suggest heat stress and recurrent dehydration as plausible factors. If this is so, the advent of global warming may lead to an even greater disease burden in the years to come.

It would be difficult to generalize the findings in this study. In Taiwan, farmers were reported to be older (average age of 68 years old) and self-employed in smaller-scale, family-based agricultural work. Older studies from Central America found younger farmers that were more commonly involved in large-scale, contracted farming. Such factors may bring a different set of occupational and heat-related risks.

In the end, the challenge remains among nephrologists to ask about occupations and heat exposure when the cause of CKD is unknown; and to apply a collaborative approach in examining clinical, epidemiological, and histological data among the different CKDu hotspots to better understand its pathogenesis, diagnose and identify the extent of the disease; as well as implement known strategies to slow the progression of CKD.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENTS

Funding

The work was partly supported by the National Health Research Institutes (Grant number: NHRI-EX112-11208PI) to M.-Y. L., and the National Science and Technology Council (Grant number: NSTC112-2314-B-037-116- and NSTC 112-2314-B-037-012-) to S.-J. H.

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