



Perspective

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Heat stress nephropathy: The emerging epidemic of chronic kidney disease of unknown etiology in tropical agricultural workers

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Chronic kidney disease is typically the slow sequel of diabetes, hypertension and age. Yet, across the hot agricultural belts of the tropics, clinicians increasingly meet its inversion: young, lean manual workers in advanced renal failure who carry none of these risk factors and spill little or no protein into their urine[1]. For more than two decades, this entity has traveled under the unsatisfying label of chronic kidney disease of unknown etiology (CKDu). A growing body of mechanistic, occupational and epidemiological evidence now converges on a single thread running through many affected regions: repeated occupational heat stress with volume depletion, the basis of what is increasingly termed heat stress nephropathy[2].

The clinical phenotype is strikingly consistent across continents (Table 1). The disease concentrates in those who perform strenuous labor in high ambient heat, usually working-age men, though women who farm are affected too; it largely spares the affluent and the sedentary, and stays silent until screening detects an already low estimated glomerular filtration rate (eGFR)[1,3]. Urinalysis is usually bland, with no or minimal proteinuria (<1 g per 24 hours)[1]. Hypokalemia, hypomagnesemia and hyperuricemia point to a tubular lesion[1], and biopsies from the two best-studied settings, Mesoamerica and Sri Lanka, show a broadly concordant core: chronic tubulointerstitial nephritis with interstitial fibrosis, tubular atrophy and glomerulosclerosis rather than a primary glomerular disease. The Sri Lankan lesion is the more heterogeneous of the two, carrying greater interstitial inflammation and vascular change[4]. That populations separated by oceans, farming different crops under different chemical exposures, should share so much renal pathology is itself a signal that a common physical insult is at work.

The proposed pathophysiology is biologically coherent. A cane cutter or paddy farmer may shed a substantial volume of hypotonic sweat in a shift, driving recurrent volume depletion and a rising core temperature[2]. Dehydration activates the vasopressin axis and a polyol pathway in which endogenous fructose, formed under hyperosmolar stress, is metabolized by fructokinase in the proximal

tubule to yield uric acid and reactive oxygen species[2,5]. Exertional hyperuricemia and low urine flow favor uric acid crystalluria, while heat and subclinical muscle injury add further tubular stress[5]. A single day's work in these hot conditions can cause an acute, subclinical decline in kidney function that likely resolves before the next shift; repeated across a harvest season, these insults may accumulate, producing a measurable drop in eGFR. The trajectory is indeed modifiable: in the intervention study, eGFR fell significantly over the course of a single harvest, with a trend toward a steeper fall in the hotter coastal group, while heavier work was associated with greater cross-shift kidney stress. A water, rest, shade, and work-efficiency intervention was associated with smaller declines in eGFR both across a working day and across the harvest, though the authors judged it premature to conclude that the program prevents kidney disease[6].

Heat is unlikely to act alone. The label of unknown etiology endures because the picture is genuinely multifactorial and regionally variable. Cadmium, arsenic, fluoride, hard water and glyphosate remain debated in South Asia, and agrochemical nephrotoxicity, leptospirosis, and the liberal use of non-steroidal anti-inflammatory drugs and sugary rehydration drinks may each lower the threshold for heat injury[1,3]. The most defensible reading is not a single cause but a multiple-hit model, in which recurrent

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Table 1. Shared and distinguishing features of the major regional forms of chronic kidney disease of unknown etiology (CKDu) in tropical agricultural workers.

Feature	Mesoamerican nephropathy (Central America)	CKDu, dry zone (Sri Lanka)	Uddanam nephropathy (India)
Typical workforce	Predominantly male sugarcane and other manual workers, often <50 years	Predominantly male rice (paddy) farmers; women also affected	Male and female rice/plantation farmers
Proteinuria	Absent or mild	Mild; tubular (↑ α_1 -microglobulin)	Absent or mild
Biochemistry	↓ K ⁺ , ↓ Mg ²⁺ , ↑ urate	↓ Na ⁺ / ↓ K ⁺ / ↓ Mg ²⁺ common	Tubular pattern
Kidney histology	Chronic tubulointerstitial nephritis; interstitial fibrosis, tubular atrophy, glomerulosclerosis	Same core lesion but more heterogeneous, with more interstitial inflammation and vascular change	Chronic tubulointerstitial nephritis
Leading proposed drivers	Recurrent heat stress and volume depletion; uric acid	Heat stress plus debated agrochemicals/metals/contaminated water	Heat and dehydration; possible agrochemical co-factors

Compiled from references 1, 3, 4 and 5. CKDu: chronic kidney disease of unknown etiology; Na⁺: sodium; K⁺: potassium; Mg²⁺: magnesium; ↑ : increased; ↓ : reduced.

heat stress and dehydration form the common denominator that local toxins and behaviors amplify. This synthesis carries practical force, converting a bewildering epidemic of unknown origin into a set of overlapping exposures that are partly occupational, and therefore partly preventable.

If heat is the engine, the epidemic is tethered to the climate. Rising ambient and, more tellingly, wet bulb temperatures are already pushing outdoor labor beyond the limits of human thermoregulation for much of the workday, and the frequency of extreme heat days is increasing[2,7]. The immense agricultural workforce of South and Southeast Asia is among the regions where dangerous heat is rising substantially, making heat stress nephropathy a plausible sentinel disease of a warming world and a particular threat across the Asia Pacific[2,7]. It is also a study in inequity: the burden falls on some of the poorest and least protected workers.

Several priorities follow for tropical medicine. Surveillance should improve, embedding eGFR measurement and urinalysis in occupational and primary care across high-risk areas, since the early disease is silent[1]. Nomenclature should sharpen; where the evidence permits, replacing unknown etiology with an exposure-anchored term such as heat stress nephropathy would focus both research and prevention. Above all, intervention need not wait for every mechanistic question to be resolved. Providing water, rest and shade, improving tools and the organization of work, shifting labor away from peak heat, and evaluating these measures rigorously at scale can begin now[6,7]. The disease is already a leading cause of premature death in affected communities. The interventions are grounded in good occupational health practice, and although the evidence is not yet conclusive, there is a strong precautionary case for acting now[1,7].

The patient who does not fit the textbook is pointing to something the textbook has yet to absorb: in a warming world, the kidney is as much an organ of occupational and environmental medicine

as it is of internal medicine. Naming heat stress nephropathy, and preventing it, may prove one of the more attainable pieces of climate adaptation now within reach.

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Authors' contributions

The author contributed to the conception, drafting, critical revision, and final approval of the manuscript.

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