Climate Change and the Emergent Epidemic of CKD from Heat Stress in Rural Communities: The Case for Heat Stress Nephropathy

Jason Glaser, Jay Lemery, Balaji Rajagopalan, Henry F. Diaz, Ramón García-Trabanino, Gangadhar Taduri, Magdalena Madero, Mala Amarasinghe, Georgi Abraham, Sirirat Anutrakulchai, Vivekanand Jha, Peter Stenvinkel, Carlos Roncal-Jimenez, Miguel A. Lanaspa, Ricardo Correa-Rotter, David Sheikh-Hamad, Emmanuel A. Burdmann, Ana Andres-Hernando, Tamara Milagres, Ilana Weiss, Mehmet Kanbay, Catharina Wesseling, Laura Gabriela Sánchez-Lozada, and Richard J. Johnson

Due to the number of contributing authors, the affiliations are provided in the Supplemental Material.

Correspondence: Dr. Richard J. Johnson, Division of Renal Diseases and Hypertension, 12700 East 19th Ave, Room 7015 Mail Stop C281, University of Colorado, Anschutz Medical Campus, Aurora, CO 80045. Email: Richard.Johnson@ucdenver.edu

Abstract
Climate change has led to significant rise of 0.8°C–0.9°C in global mean temperature over the last century and has been linked with significant increases in the frequency and severity of heat waves (extreme heat events). Climate change has also been increasingly connected to detrimental human health. One of the consequences of climate-related extreme heat exposure is dehydration and volume loss, leading to acute mortality from exacerbations of pre-existing chronic disease, as well as from outright heat exhaustion and heat stroke. Recent studies have also shown that recurrent heat exposure with physical exertion and inadequate hydration can lead to CKD that is distinct from that caused by diabetes, hypertension, or GN. Epidemics of CKD consistent with heat stress nephropathy are now occurring across the world. Here, we describe this disease, discuss the locations where it appears to be manifesting, link it with increasing temperatures, and discuss ongoing attempts to prevent the disease. Heat stress nephropathy may represent one of the first epidemics due to global warming. Government, industry, and health policy makers in the impacted regions should place greater emphasis on occupational and community interventions.

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One of the pressing challenges facing the world is the increasing impact of climate change and water shortage (driven by both climate change and population expansion) on human health and productivity. Global warming has resulted in an overall increase of about 0.8°C during the last century, and is estimated to be responsible for 75% of the extreme heat events (1–4). Heat waves typically refer to sustained temperatures of >40°C, or temperature increases of >5–6°C over the normal maximum temperature of the region, or any time temperatures reach >45°C (5–7). One of the most intuitive effects of heat waves on human health is heat stroke and death. During the summer of 2015, for example, the heat index—which takes into account both air temperature and humidity—toppled world records at 74°C (165°F) in Iran. A heat wave in Pakistan resulted in 40,000 cases of heat stroke, and another heat wave in Andhra Pradesh took 1400 lives in 1 month (8–10). Conditions will worsen, with predictions of a rise of 3–4°C in mean temperature by the end of the century (11), which could result in intermittent temperatures incompatible with outside living in some of the hottest areas of the world, such as the Middle East (12). The rise in temperature is paralleled by an increasing shortage of water, with the percentage of the world population suffering from moderate water shortage (defined as 1.0–1.7 m^3 water/person per year) skyrocketing from 5% in 1800 to 50% in 2005, and with 10% of the world population currently suffering from extreme (<0.5 m^3 water/person per year) water shortage (13).

While increased risk for heat stroke is an obvious manifestation of global warming, climate change affects health in many other direct and indirect ways (14,15). Dehydration secondary to heat stress (relative water loss with development of hyperosmolarity) is associated with cognitive dysfunction, hypotension, and AKI (16). Drought can reduce crop yields, which can lead to starvation, malnutrition, and act as a threat multiplier to poverty and violence, especially in regions of the world with poor governance; likewise, extreme heat waves kill heat-sensitive cereals such as wheat and rice (17–19). Alterations in water supply, with variations in precipitation, can lead to emergence of water-borne and vector-borne infectious diseases (20,21). Drying up of wells can lead to increased concentration of heavy metals and/or toxins. Furthermore, subjects who are chronically dehydrated may not excrete toxins as effectively as those who are well hydrated, leading to higher concentrations of toxins in the serum and kidney. In addition, chronic dehydration and hyperosmolarity have also been linked with increased risk for obesity, diabetes, and metabolic syndrome (22,23). Thus, a wide variety of health issues are likely to result from climate change over the next century, emphasizing the importance for educating physicians, industry, policy makers, and the public.

Recently, an epidemic of CKD of unknown etiology has been recognized in Central America (Mesoamerican nephropathy), which has been linked with recurrent dehydration and heat stress (24–26). We and others have previously suggested, based on both experimental and epidemiologic studies, that this disease may be a type of heat stress nephropathy (HSN) and could be an example of a disease that is accelerated by global warming (27,28). If true, one might hypothesize that similar epidemics should be occurring among those working manually in other hot environments. Unfortunately, the subjects at risk are often from impoverished and neglected populations where medical care is poor, renal biopsies are rarely performed, and diagnosis is rarely confirmed. Nevertheless, there are reports of CKD of unknown etiology emerging in other regions of the world where individuals are performing strenuous manual labor under very hot conditions (29–31).

Here, we provide a brief summary of these epidemics, and evaluate the relationship to heat stress, local environmental changes (global warming and progressive water shortages), and dietary changes (increased sugar intake). Although surveillance data are limited, the populations identified as most at risk are heavy laborers with a high workload, limited access to potable water, and otherwise extreme working conditions (32–34). We propose that HSN may be a major cause of CKD, representing an overlooked disease in neglected populations in hot communities. We suggest it may also emerge as a cause of CKD in any population where subjects are exposed to heat stress.

Mesoamerican Nephropathy

Mesoamerican nephropathy was first reported in 2002 in El Salvador by one of the authors (R.G.T.) during his medical residency, when excessive numbers of individuals were presenting at Hospital Rosales in San Salvador with ESRD (35). The disease typically presents in male sugarcane workers from the Pacific coast of Central America, but has since been reported with less frequency in other occupations, including in construction workers, corn and rice farmers, cotton plantation workers, and miners (32,36–38). In the affected areas women also have an increased prevalence of CKD, although to a much lesser extent, and there is some preliminary evidence that children from these regions may also be at risk (36,39,40). Clinically, the subjects are usually discovered with an asymptomatic rise in serum creatinine, in association with low grade or absent proteinuria, occasionally with microhematuria (36,37). Mild anemia, hypokalemia, and hyperuricemia are common (41–43). Renal biopsies show interstitial fibrosis, low grade inflammation, tubular atrophy, and extensive glomerulosclerosis with signs of glomerular ischemia but only mild vascular lesions (42,44). Progression to ESRD occurs over several years and is higher in those who work more harvests (32). Since chronic renal replacement programs are rarely available in the affected regions, many thousands have died (25).

Initial concerns were that Mesoamerican nephropathy might be due to a toxin, for example, from exposure to agrochemicals (such as glyphosate), heavy metals (such as from lead, cadmium, or arsenic), or infectious agents (such as leptospirosis) (24,45,46). The theory that this was a result of direct exposure to pesticides in the fields, however, is weakened by the presence of the disease in occupations not involving farming, by reports that there is a greater risk for renal injury in the sugarcane fields among the cane cutters as opposed to the pesticide applicators, and because the frequency of the disease is lower in sugarcane cutters working at higher altitudes where it is significantly cooler than at lower altitudes, despite similar agrochemical exposure (32,36,47). Nevertheless, it remains possible that toxins, for example, could be concentrating in well water that could affect the populations as a whole. There is also minimal evidence for heavy metal poisoning, such as from lead or cadmium (29). Nonsteroidal agent use is also common among the sugarcane workers and could be an additive factor, but several studies could not identify nonsteroidal anti-inflammatory drugs as an independent risk factor for CKD in this population (32,36,48). Infections, such as leptospirosis, remain a possible cause (49) but there is minimal evidence for this disease as a primary driver of this epidemic, and certainly some manifestations of leptospirosis, such as liver involvement, are not observed.

HSN: The Cause of Mesoamerican Nephropathy?

The Pacific coast is one of the hottest regions in Central America and aligns closely with the location of the epidemic (Figure 1). As the effects of heat are compounded by humidity and other factors, heat exposure is commonly measured by the wet bulb globe temperature (WBGT), a composite index that includes air temperature, solar radiation (globe temperature), wind speed, and humidity (50). For outside workers the Occupational Safety Health Administration recommends frequent work breaks (15 minutes per hour) for a WBGT of 26°C and breaks of 45 minutes per hour for a WBGT of ≥30°C, whereas at temperatures >35°C humans cannot maintain their body temperature by usual mechanisms (sweating) for >6 hours (12,50,51).

Sugarcane workers are particularly at risk for heat stress and dehydration due to the heavy exertion, lack of shade, infrequent breaks, long work hours (in some regions), and lack of access to sufficient potable water during the workday (50,52). Sugarcane is often burned to facilitate cutting and, depending on the local policy, some sugarcane workers enter the fields the morning after the burning, where they may be exposed to additional heat from the recently burned cane. While work begins in the early morning when the temperature is relatively cooler, the WBGT often surpasses 28°C by midmorning (53). As such, many subjects show symptoms of heat stress and dehydration when in the fields (headaches, lightheadedness, and fainting), and during the work shift their systolic and diastolic BP falls, pulse rises, and urine becomes progressively concentrated and acidic due to the activation of the renin-angiotensin-aldosterone system, with a loss of hydrogen and potassium in the urine (50,54).

Evidence that heat stress and recurrent dehydration may be the cause of Mesoamerican nephropathy is emerging. Acute dehydration is generally considered to be a reversible type of kidney failure (termed ‘prerenal’) that responds to

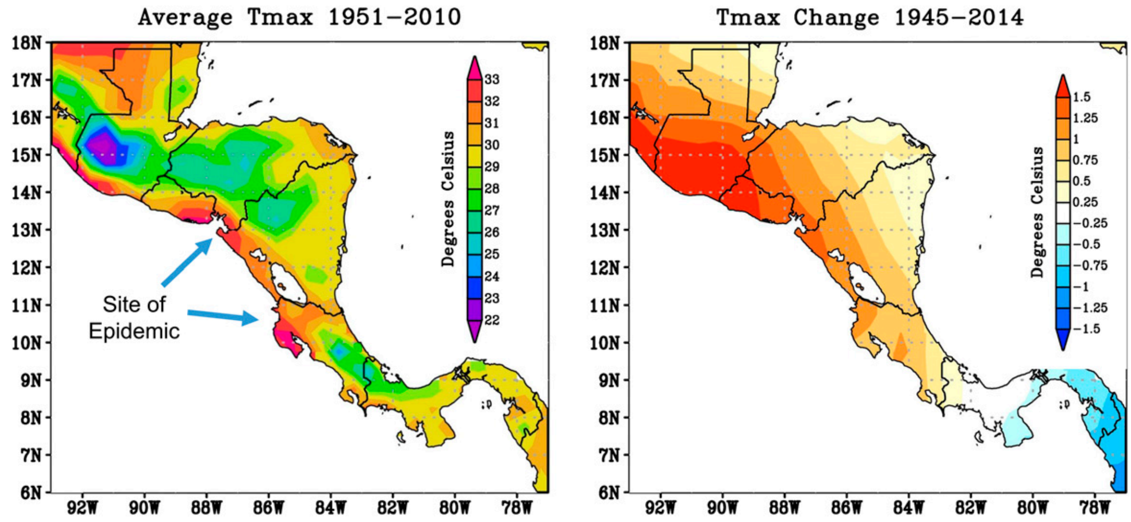

Figure 1. | **Temperature trends in Central America**. The average maximum temperatures (Tmax) in Central America over the last 60 years (left panel) correspond closely with sites of the CKD epidemic, such as Chichigalpa and Quezalguaque in Nicaragua, San Alejo and the Bajo Lempa region in El Salvador, or Guanacaste in Costa Rica. Those areas are also generally colocated with the climatologically warmest zones (left panel). Maximum temperatures are also increasing, especially in Guatemala and El Salvador (right panel). Data from the US National Oceanic and Atmospheric Administration, Earth System Research Laboratory, Boulder, Colorado (public domain). Average daily Tmax at observing sites are averaged into monthly, and then into annual mean values. Data are then objectively interpolated to a half-degree grid. The left panel shows the 60-year (1951–2010) annual average, and the right panel shows the total linear trend change over the period 1945–2014.

rehydration. However, there is an interesting report of four Bantu gold miners who developed heat stroke with AKI that recovered only to later present with CKD due to chronic interstitial fibrosis (55). Experimental studies in mice have also demonstrated that recurrent daily heat exposure and dehydration can cause chronic tubulointerstitial disease with fibrosis and inflammation, similar to what is observed in renal biopsies of subjects with Mesoamerican nephropathy (56). Interestingly, renal injury is largely prevented if rehydration is given between exposure to heat/dehydration, as opposed to at the end of the day, despite equivalent amounts of water provided. This mirrors conditions in the fields where workers often only rehydrate at lunch and at the end of the workday. The mechanism has been linked with development of hyperosmolarity with activation of the vasopressin and aldose reductase/fructokinase pathway (56,57). Recurrent dehydration, for example, activates aldose reductase in the proximal tubule, converting glucose to fructose that is metabolized by fructokinase in the proximal tubule, leading to the release of oxidants that cause local tubular injury (56). Vasopressin has also been shown to accelerate experimental CKD (58,59). In turn, repeated AKI may lead to CKD (60).

Dehydration and recurrent volume depletion may also cause CKD *via* other mechanisms (Figure 2). For example, volume depletion can lead to hypokalemia, which causes intrarenal vasoconstriction and hypoxia, resulting in chronic tubulointerstitial injury (61). Hypokalemia is common among sugarcane workers presenting with CKD (41–43). Nevertheless, the tubular vacuolation common in hypokalemic nephropathy (61) has not been reported. Heat stress-associated labor can also result in subclinical or clinical rhabdomyolysis from low grade muscle trauma and heat, and has been shown to occur during the work shift in sugarcane workers (34). Rhabdomyolysis is a well known cause of AKI (62), and repeated exposures may lead to CKD. Finally, hyperuricemia and uricosuria associated with heat stress may lead to excessive levels of uric acid in the urine, which may also crystallize in the urine, and this has also been documented in the affected sugarcane workers (28). Indeed, many subjects complain of intermittent dysuria from the passage of sand-like material (termed *chistata* in Nicaragua and *mal de orín* in El Salvador) due to urate crystalluria, and this is frequent in sugarcane workers and is associated with signs of dehydration (50,63,64).

Studies in Costa Rica have shown that Mesoamerican nephropathy was probably present in the 1970s in the Guanacaste province on the Pacific coast, yet the prevalence had increased almost ten-fold in men and four-fold in women by 2010 (39). During this same time, the maximum temperatures in Central America had risen by 0.8°C–1.0°C (Figures 1 and 3). While the mean rise in temperature may seem small, temperature extremes (the number of extremely hot days) increased by 30%–75% (1). During the sugarcane harvest, maximum WBGT often surpasses the 30°C limit by 10:30 a.m., especially during the late harvest of April and May, with levels >35°C being occasionally recorded (41,50). Thus, the risk for recurrent dehydration is likely greater on these hot days. Consistent with this possibility, in a study in which uric acid was measured before and after work on four different dates during a sugarcane harvest, we noted one day in which all seven worker samples available showed extremely high uric acid levels (>100 mg/dl) compared with the other dates, and this was one of the hotter days of the year (May of 2013) (65).

We propose that Mesoamerican nephropathy is more frequent in sugarcane workers as they are working in the most extreme conditions, as noted by heat exposure and work intensity (66). Indeed, one study found that the greatest risk for Mesoamerican nephropathy in El Salvador

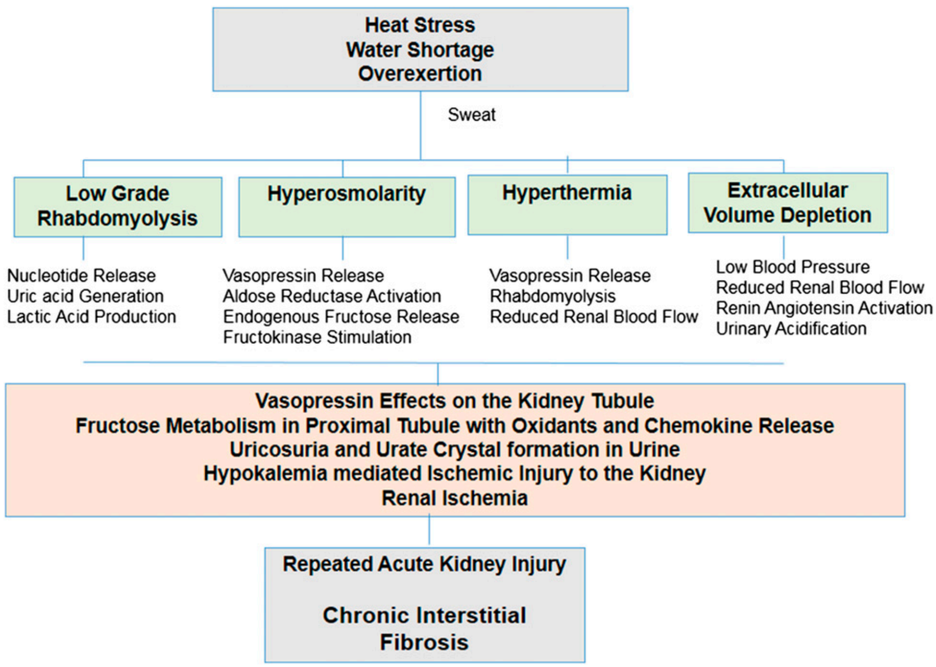

Figure 2. | **Mechanism for heat stress nephropathy**. Repeated heat stress and water shortage, especially when coupled with overexertion, can lead to several pathophysiologic processes, including low grade or overt rhabdomyolysis, hyperosmolarity, hyperthermia, and extracellular volume depletion. These processes can result in several mechanisms that can lead to AKI, including the acute effects of vasopressin on renal tubules, endogenous fructose metabolism in the proximal tubule *via* the fructokinase system, the development of uricosuria and urate crystal formation, hypokalemia-induced renal vasoconstriction and injury, and a generalized reduction in renal blood flow that may also cause ischemic damage. Repeated AKI, in turn, may lead to chronic tubulointerstitial disease.

was working in sugarcane fields, with the second greatest risk factor being working in areas of high mean maximum temperature (67). However, all individuals spending time in the hot external environment, or indoors without sufficient ventilation, might be at risk, potentially explaining why there is some evidence for the presence of renal injury in other occupations, in women, and possibly in children. While the rise in disease prevalence may be due, in part, to improved diagnosis and surveillance, there is likely a true rise in incidence that correlates with climate change. Inadequate hydration is also a key factor, as some subjects are afraid of drinking well water as it may contain toxins, and others drink fructose-containing sugary beverages (juices and soft drinks) that may exacerbate the renal injury (56). Laboratory rats with heat-associated dehydration show worse renal damage if they are rehydrated with sugary beverages as opposed to water (68). Finally, there may be higher risk in sugarcane workers than in the past, as the practice of burning cane prior to harvesting was enacted only in the last few decades and this has also led to an increase in the average number of tons cut by workers in a given day. These environmental and land use factors are exacerbated by greater demands placed on sugarcane cutters, as they are paid by piece. While definitive data for Central America is lacking, a study in Brazil reported that sugarcane workers are required to cut three to four times as much as they did 20 years ago (69).

Sri Lanka Nephropathy

A similar epidemic of CKD of unknown etiology is ongoing in the northern provinces of Sri Lanka (70–73). The epidemic has been increasing since the 1980s, and currently affects more than 100,000 individuals (74). The primary population affected are young to middle-aged male rice farmers, although women working in the fields are also at risk (73,74). The CKD is clinically similar to that observed in Central America, with most subjects presenting with asymptomatic elevations in serum creatinine with normal BP and minimal proteinuria, or with the individuals discovered to already be in ESRD. Biopsies show chronic tubulointerstitial disease (75).

The etiology of Sri Lanka nephropathy remains unknown. The association of the disease with drinking well water (76) has led to concerns of toxin exposure, such as from heavy metals (cadmium and arsenic) or agrochemicals (71). While an early study linked cadmium exposure with the CKD (72), more recent studies have found minimal evidence for cadmium or other heavy metal exposure, with levels in both deep and surface wells within acceptable limits (77,78). Exposure to agrochemicals, such as glyphosphate, remain possible and some studies suggest that the disease may represent an aggregate of nephrotoxins as opposed to a single entity (71). Nevertheless, concerns that the wells are contaminated may encourage farmers not to drink local water and could predispose them to increased risk for dehydration. The Northern Province is the hottest region in Sri Lanka (Figure 4). Indeed, in one study in which 100 subjects with CKD were compared with control subjects, the risk for CKD was higher in those exposed to the sun, those working for >6 hours, and those drinking <3 L of water per day (risk increased between fourfold and eightfold), and this was also

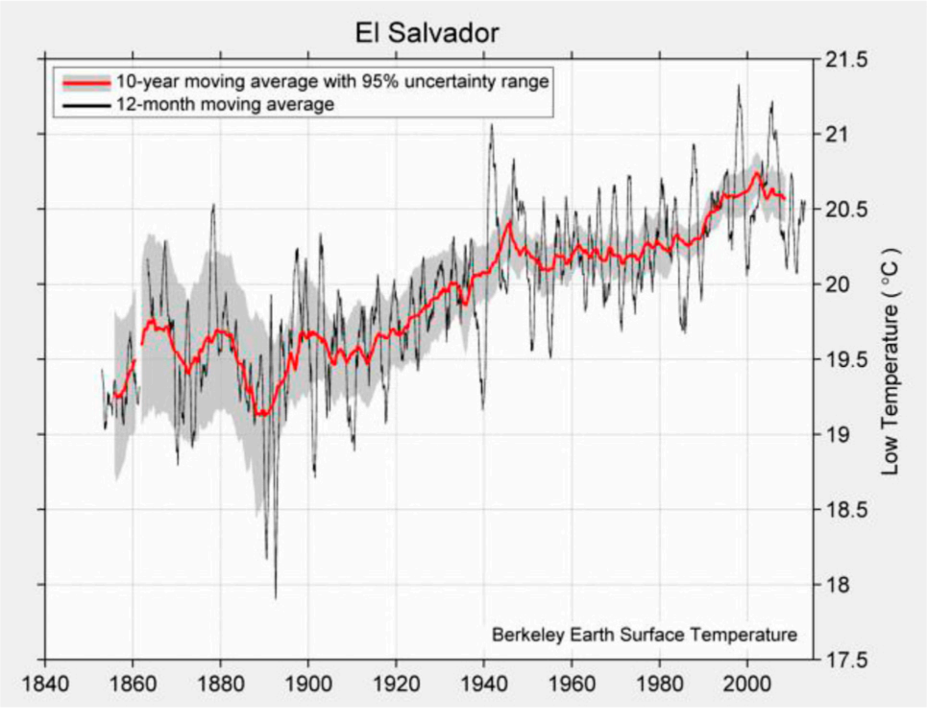

Figure 3. | **Changing temperatures in El Salvador**. Mean temperatures have increased by about 0.8°C during this period in El Salvador, which results in a significant (30%–75%) increase in the frequency of extremely hot days (>99th percentile) (image from Berkeley Earth [http://berkeleyearth.lbl.gov/regions/el-salvador], public domain).

associated with the presence of dysuria at the end of the work day that cannot be ascribed to urinary tract infection (76). Similar to the situation in Central America, many subjects with CKD also have hyperuricemia (mean levels of 7.2 mg/dl versus 5.2 mg/dl in controls) and hypokalemia (Channa Jayasumana, personal communication).

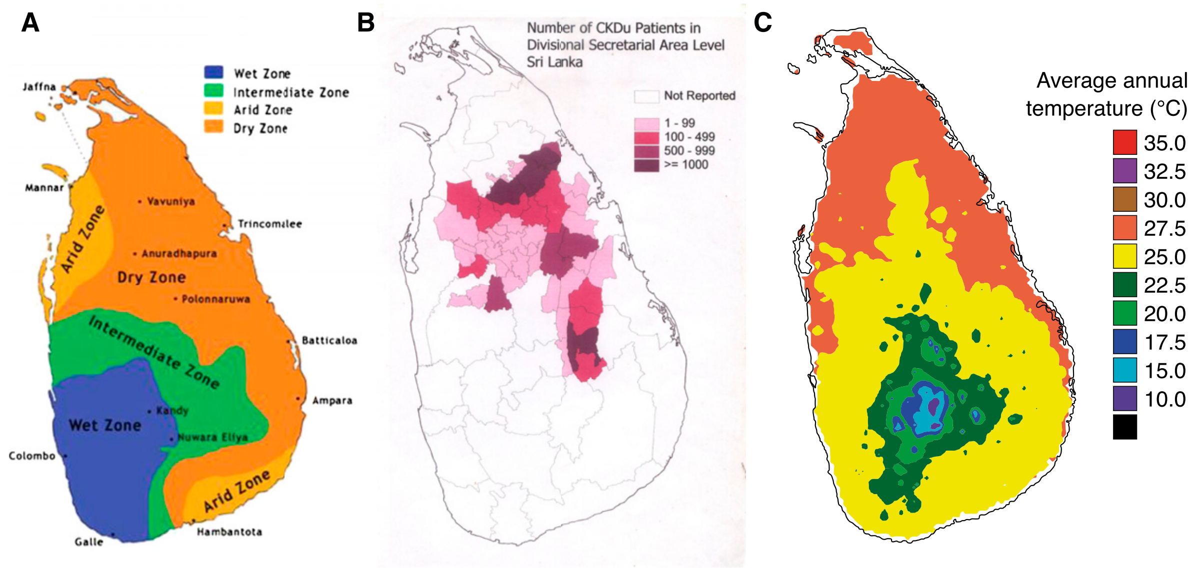

Figure 4. | **Sri Lankan nephropathy**. (A) and (B) An epidemic of CKD is occurring in the dry zone of the north central region of Sri Lanka. (C) The region is exceptionally hot, with average temperatures of approximately 30°C. While the relationship of CKD with higher average annual temperatures is evident, it is interesting that the most northern part of Sri Lanka is also hot but does not appear to be a site of the CKD epidemic. However, this is an area where little investigation has been done, and it remains possible to be a site of under-reporting. (A) and (B) courtesy of Channa Jayasumana (106). (C) is from the Centre for Climate Change Studies, Department of Meteorology, Colombo, Sri Lanka (http://www.meteo.gov.lk/index.php?option=com_content&view=article&id=13&Itemid=132&lang=en). CKDu, CKD of unknown etiology.

The Epidemics of CKD in India

An epidemic of CKD in rural farmers (of rice, coconuts, and cashews) in Andhra Pradesh, India, was first observed by one of the authors (G.T.). A study of 1500 villagers in the Prakasham district documented 27% with serum creatinine levels >1.5 mg/dl, with 60% having an eGFR of <60 ml/min per 1.73 m^2 (30,79). Studies based on sites where hemodialysis is present suggest even higher rates in the Nellore District to the south, and represent rates that are about tenfold higher than in other regions of India. Similar to Mesoamerican nephropathy, the disease is observed primarily in hot, rural communities in which the primary occupation is farming. Most subjects present late and renal biopsies are not done; however, when performed they show chronic tubulointerstitial disease, with many of the features suggesting a similar disease as Mesoamerican nephropathy, including an asymptomatic rise in serum creatinine with minimal proteinuria, in the absence of diabetes and hypertension. Furthermore, many of these subjects give a history of recurrent dehydration and frequent hyperuricemia (Gangadhar Taduri, personal communication). Similar to Mesoamerican nephropathy, there is also some evidence that this disease has been present for decades but has increased in recent years. Indeed, Mani reported in 1993 that chronic tubulointerstitial nephritis (diagnosed based on clinical presentation of small kidneys with no history of edema, minimal proteinuria, and an absence of diabetes and hypertension) was the most common cause of CKD in his unit in Madras, especially among the rural farmers of the area, where it constituted 40% of all cases of CKD (80).

India has experienced rising temperatures over the last century, with a mean annual rise of 0.8°C in the last 100 years (81). This has been associated with a 10.4% decrease in annual rainfall over the last century (1901–2007), with a 17.6% decrease in annual rainy days over the same period (81). Whereas traditionally, the farmers living in rural areas relied on surface water from lakes, ponds, and shallow

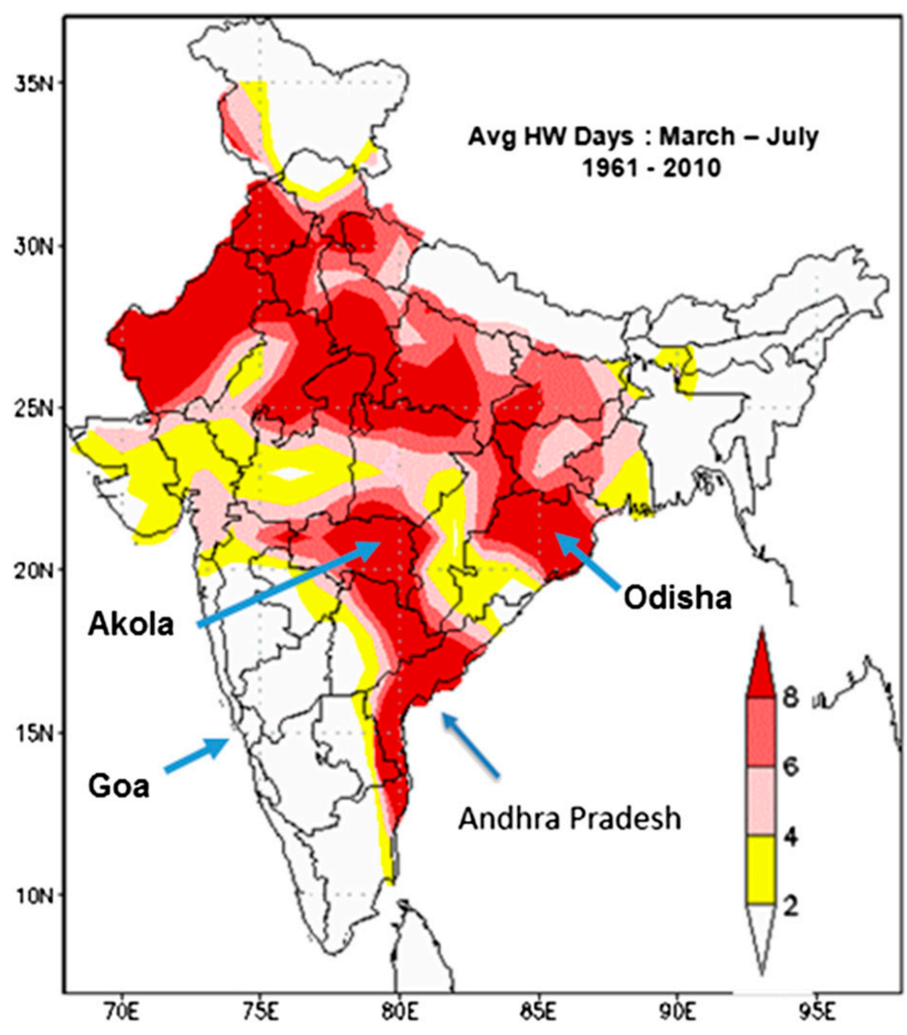

Figure 5. | **Confirmed site (Andhra Pradesh) and suspected sites of CKD epidemics of unknown etiology in India**. Average number of heat wave days (Avg HW days) between March and July (hottest time of the year) in India, based on the number of heat wave days over the 50-year period. Andhra Pradesh has had some of the longest heat waves, with one recorded at 35 days. Other suspected sites of CKD of unknown etiology, such as the Akola district of Maharashtra and the central Odisha region, are also sites with high number of heat waves. In contrast, Goa does not show this pattern. Courtesy: Editor Mausam—India Meteorological Department. Reprinted from reference 5, with permission.

wells as their source of drinking water, there has been a shift toward drinking ground water that in some rural areas, such as Andhra Pradesh, is becoming increasingly limited due to inferior quality and decreasing groundwater tables (82). In Andhra Pradesh, the number of heat wave days during spring has increased markedly, with one heat wave lasting 35 days (Figure 5), and this is associated with an increase in heat strokes and mortality (5). Climate projections for the 21st century also show a nationwide increase in temperature, heat waves, and heat stress-related mortality (83). The minimum temperatures have also been increasing in recent decades and are projected to increase over the Indian subcontinent (83). This reduces the nighttime cooling that is typically available, thereby increasing hydration stress, and can also reduce crop yield, especially rice.

Other Hot Spots of CKD

South Asia

Other areas with CKD of unknown etiology are slowly being recognized (Table 1). For example, there are reports of CKD epidemics in other areas of India, including Goa, some regions in central Odisha, and Akola districts in Maharashtra (Vivek Jha, personal communication). This seems consistent with increased occurrence of heat waves and decreased rainfall in these regions (5) (Figure 5). CKD of undetermined etiology is also one of the dominant causes of ESRD in Thailand, accounting for 20%–25% of causes of ESRD (84,85). CKD of unknown etiology is highest in the northeastern (Isan) region, which is one of the hottest regions in Thailand. These subjects also show signs of recurrent dehydration, with the presence of hypokalemia, hyperuricemia, acidic urine, and passage of sand-like material with dysuria similar to that observed in Central America (Amorn Premgamone, personal communication) (86,87). These observations are consistent with epidemiologic studies in Thailand linking excessive CKD with occupational heat stress (88) and hyperuricemia (89).

North and South America

Back to the Americas, there are similar reports of excessive CKD of unknown etiology in Mexico, in the rural region of Tierra Blanca, Veracruz (90). Tierra Blanca has the hottest climate in Veracruz State and most of the agricultural activities include sugarcane, lime, cantaloupe, papaya, rice, mango, and bananas. The National Cardiology Institute in Mexico City has been a referral center for this population, and 58 kidney transplants from this area have been done in the past 5 years. These patients are typically young men (mean age, 29 years) with no traditional risk factors for CKD. A recent analysis in this area reported that the prevalence of CKD was 15%–25% in males aged 20–39 years old, and the death certificates from CKD report 32–77 per 100,000 deaths per year, with 20% of the deaths occurring in subjects <40 years old (91). AKI has also been reported in sugarcane workers in Brazil (34), and population-based studies are being planned in Brazil to better understand the clinical and epidemiologic situation on the ground.

There have also been reports that farm workers, most of whom are migrants, may be developing acute kidney disease and CKD at higher rates than expected in the Central Valley of California (92,93). One recent study linked hospitalizations for dehydration and AKI with the onset of heat waves in the Central Valley and other hot regions in California (94). Further studies are required to better characterize the prevalence and clinical characteristics of the CKD, but it is worrisome that it may be similar to what is occurring with farmers in other hot, rural environments. Clinicians in California and Texas have also reported immigrants from Mexico and Central America with work histories and clinical characteristics consistent with the profile of the disease outlined in this paper (David Sheikh-Hamad, personal communication).

Table 1. Confirmed and suspected sites of heat stress-associated nephropathy (CKD)

Country	Region	Reference
Confirmed Sites		
Central America		
Costa Rica	Guanacaste	Wesseling *et al.* (39)
El Salvador	Bajo Lempa	Orantes *et al.* (45)
Guatemala	Southwest Region	Laux *et al.* (105)
Nicaragua	León and Chinandega	Torres *et al.* (36)
South Asia		
India	Andhra Pradesh	Reddy and Gunasekar (79), Abraham *et al.* (30)
Sri Lanka	North Central Region	Jayatilake *et al.* (72) Jayasumana *et al.* (106)
Possible Sites		
South Asia		
India	Goa, Odisha, and Maharashtra	Rajapurkar *et al.* (107)
Thailand	Northeast (Isan Region)	Sirirat Anutrakulchai (personal communication)
Middle East		
Saudi Arabia	Tabuk region	El Minshawy *et al.* (108)
Africa		
Egypt	El-Minia, Upper Egypt	El Minshawy *et al.* (96)
Sudan	Southern Sudan	Elamin *et al.* (109)
North America		
Mexico	Tierra Blanco, Veracruz	Mendoza-González *et al.* (90)
United States	California Central Valley	Moyce *et al.* (93)

Notably, the Migrant Clinicians Network has initiated a survey to determine if HSN may be occurring among migrant workers in the United States (95).

Africa and the Middle East

In northern Africa and the Middle East, ESRD has been reported to be high in rural farm workers in El Minya in Upper Egypt (27% of cases) (96,97) and in the Tabuk area of Saudi Arabia (33% of cases) (96). Further studies are needed to address the role of heat stress and dehydration in these disorders and their relation to climate change and water supplies. Less is known about the etiology of ESRD in sub-Saharan Africa, in part because of the rarity of renal biopsy and poor overall reporting (98).

General Mechanism for CKD

In addition, the observation that recurrent dehydration may cause CKD also suggests that chronic dehydration or intermittent hyperosmolarity may also have a role as a general risk factor for CKD of traditional causes (57). It is interesting that both low water intake and low urinary pH have recently been identified as risk factors for CKD progression, and some studies suggest that bicarbonate therapy may slow renal disease, which might act by alkalinizing the urine and reducing uric acid crystal formation (99–101).

Possible Low Cost Treatment Opportunities

Prevention of HSN should focus on improving hydration and worksite practices. Given that hyperuricemia and uricosuria is common, lowering uric acid may also provide a low cost treatment opportunity. There is increasing evidence that lowering uric acid in hyperuricemic subjects can slow the progression of CKD (102,103). Noticeably, allopurinol was reported to slow renal disease progression in a cohort of patients from Andhra Pradesh, of which 25%–30% had CKD from chronic tubulointerstitial disease (104). As scale and scope of this disease grows due to improved surveillance, a warming world, increased work demands, and an increasing informal labor sector that produces more precarious populations, the costs associated with treatment and loss of productivity for countries, and industry, are likely to be enormous. Prevention, early diagnosis, and cost-effective treatment are paramount.

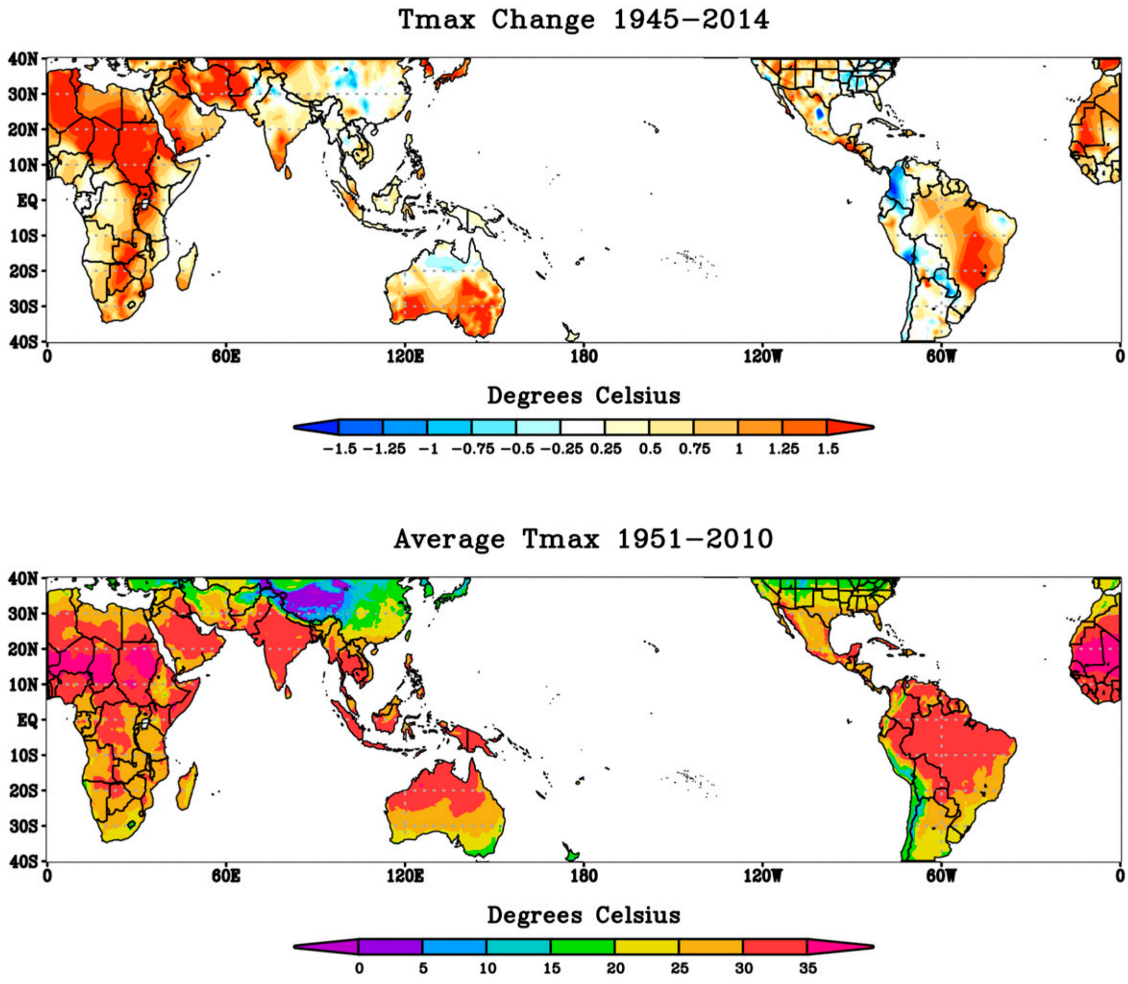

Figure 6. | **Worldwide annual maximum temperature changes**. Change in annual maximum temperature from 1945 to 2014 (top panel) and the average annual maximum temperature during 1945–2010 (bottom panel). From the US National Oceanic and Atmospheric Administration, Earth System Research Laboratory, Boulder, Colorado (public domain). Data definition as shown in Figure 1. EQ, equator; Tmax, annual maximum temperature.

Limitations

While the epidemics of CKD in Central America, India, and Sri Lanka are associated with recurrent heat stress and dehydration, more studies need to be performed to address if this mechanism is causal and whether similar processes are occurring at other sites (Table 1). Based on temperature patterns, we predict that similar epidemics of CKD from HSN may be ongoing and potentially discoverable in the hotter regions of Africa and the Middle East. However, it is important to recognize that toxicity from agrochemicals, heavy metals, and nonsteroidal anti-inflammatory drugs remain potential contributing factors. It is also important to recognize that reports of CKD of unknown etiology do not in themselves support the presence of HSN, but rather require epidemiologic studies investigating the role of heat stress and recurrent dehydration as risk factors. It also remains possible that some of the "epidemics" may represent improved awareness and diagnosis rather than a new epidemic. Nevertheless, temperature maximums are increasing, especially in the equatorial zone. Figure 6 shows the change in maximum temperature between 1945 and 2014, which indicates an increase in the hot spots discussed above–South India, Sri Lanka, and Central America. The temperature increase in recent decades and in the future also leads to evaporative loss of water that will compound the reduction in water availability.

Summary

CKD that is not associated with traditional risk factors appears to be increasing in rural hot communities in association with a progressive rise in worldwide temperatures. The disease is a type of chronic tubulointerstitial disease that has only recently been recognized, and we propose that it may be due to heat stress (HSN). We believe the risk for HSN has been increased as a consequence of global warming and an increase in extreme heat waves. We further suggest this disease has a disproportionate impact on vulnerable populations, *i.e.*, agricultural workers. Warmer temperatures, coupled with decreasing precipitation, exacerbate this epidemic by reducing water supply and water quality. We recommend epidemiologic and clinical studies to document the presence of these epidemics, their magnitude, and the role of dehydration and hyperosmolarity. A coordinated effort by governments and researchers to improve surveillance must be undertaken so we may understand the scale of the epidemic. Ongoing occupational interventions, such as the Worker Health and Efficiency Program in El Salvador (https://laislafoundation.org/the-we-program-we-can-end-ckdnt-video/), and actions by the government to improve worksite conditions (such as adequate breaks for rest and adequate clothing) should be continued. Improved hydration, alkalinization of the urine, and the lowering of uric acid may represent new approaches for the prevention and treatment of this type of CKD.

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Disclosures

R.J.J. has several patents and patent applications related to lowering uric acid or blocking fructose metabolism in the treatment of metabolic diseases. R.J.J. and M.A.L. are also members of a startup company, Colorado Research Partners LLC (Aurora, CO), which is trying to develop inhibitors of fructose metabolism. All other authors declare no conflicts of interest.

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J.G. and J.L. contributed equally to this work.

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