REVIEW ARTICLE

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Chronic Kidney Disease of Unknown Cause in Agricultural Communities

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In recent years, numerous cases of chronic kidney disease have emerged among agricultural workers, as well as among others performing manual labor, in various regions of the world. The disease does not appear to be due to the classic causes of kidney disease (e.g., diabetes, hypertension, and glomerular disease). In this review, we describe the clinical presentation and epidemiology of chronic kidney disease that is endemic in this workforce in these areas, as well as possible causes. The disease is strongly associated with working and living in a hot environment, but whether the cause is a toxin, an infectious agent, a heat-associated injury, or a combination of factors is not yet known. We also discuss some of the assumptions and limitations in our understanding of chronic kidney disease in agricultural communities.

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Regional Chronic Kidney Disease Among Agricultural Workers

Mesoamerican Nephropathy

During the 1990s, clinicians in Central America noted that a large number of young sugarcane workers were presenting with end-stage kidney disease. An early report on an upsurge in chronic kidney disease in Central America came from El Salvador in 2002.[1] One striking finding was that the patients, once evaluated, did not have any of the conditions known to cause end-stage kidney disease, such as diabetes, hypertension, or glomerular disease. Within a short time, multiple reports confirmed higher-than-expected rates of chronic kidney disease among sugarcane workers and other agricultural workers who were laboring in the fields along the Pacific Coast of Central America, from Guatemala to Panama,[2-5] and the name Mesoamerican nephropathy was proposed for the disorder.[6,7]

In retrospect, there is evidence that the condition actually emerged earlier, in the 1970s, and that the prevalence has been increasing.[8] The mortality rate among patients who present with established chronic kidney failure is high and continues to rise; as of 2012, an estimated 20,000 deaths were attributable to the disease.[9] The condition accounts for the highest rates of death from kidney disease in the world, with a rate in El Salvador that is more than 10 times that in the United States.[10]

Although the reported prevalence is highest among sugarcane workers, the condition also develops in other members of poor agricultural communities,[11] including cotton and corn workers and shrimp farm workers, as well as workers in industrial settings such as construction sites and mines.[2,5,12,13] The disease is more common among those working at sea level and is less common among sugarcane workers and almost absent among workers on coffee plantations at higher elevations.[2,5,14-16] Milder and less frequent manifestations of kidney disease have also been observed in women and children living in the region.[17-19]

Affected sugarcane workers are usually discovered to have an elevated serum

creatinine level when they undergo screening before working in a seasonal harvest (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Those affected are usually men who have worked for two or more seasons, are between 20 and 50 years old, are asymptomatic, and have normal or only slightly elevated blood pressure and normal blood glucose levels. The urinalysis shows no or minimal proteinuria (<1 g per 24 hours), small numbers of red cells and leukocytes, and occasionally amorphous urate crystals. Serum electrolyte abnormalities may include hypokalemia, hyponatremia, and hypomagnesemia in association with increased urinary electrolyte losses.[20,21] Hyperuricemia is common but not required for the diagnosis.[12,20,22] A report on a case series involving a total of 46 patients also noted evidence of vascular disease in the legs and neurologic findings, including sensorineural hearing loss (in 56.5% of the patients) and myoclonus (in 6.5%).[20]

In some sugarcane workers, serum creatinine levels have increased during the work shift, often accompanied by mild elevations in muscle enzyme levels (e.g., creatine phosphokinase), although only rarely in the range associated with clinical rhabdomyolysis.[15,23-27] It is possible that in some cases the asymptomatic rise in serum creatinine levels represents a dehydration-related decrease in renal perfusion without structural injury or that the rise in the creatinine level does not represent a true fall in the estimated glomerular filtration rate (eGFR). However, there is concern that changes in the creatinine level during the work shift may represent injury to the kidneys, which, if repetitive, could confer a predisposition to chronic kidney disease.[27,28] Indeed, one report hinted that episodes of acute kidney injury during the work shift were associated with a trend toward worsening of kidney function over the course of the harvest season,[23] and another report noted that some sugarcane workers with new elevations in the serum creatinine level (median, 1.64 mg per deciliter [145 μmol per liter]) at the end of the harvest season did not fully recover during the following year, resulting in one third with chronic kidney disease (eGFR, <60 ml per minute per 1.73 m^2 of body-surface area).[29] However, whether the development of chronic kidney disease results from repetitive acute kidney injury or represents a chronic disease process in which fluctuations in renal function over the course of a workday are exaggerated responses to changes in hydration status is not known.

Some workers have been reported to present with acute nausea and vomiting, headache, muscle weakness, back pain, and fevers after working in the sugarcane fields. These patients had elevated serum creatinine levels (mean level, 2.0 to 2.5 mg per deciliter [177 to 221 μmol per liter]), often with a neutrophilic leukocytosis with leukocyturia and low-grade microscopic hematuria. Acute interstitial nephritis was noted in many of the patients who underwent kidney biopsy.[30-32] Progression to chronic kidney disease occurred in 49 (8.4%) of 586 sugarcane workers with acute kidney injury, with a median eGFR change of −33.3 ml per minute per 1.73 m^2 from baseline normal kidney function 8 months earlier.[32] However, no comparison was made with the incidence of chronic kidney disease in a group of similar workers who did not have a history of acute kidney injury. Further assessment is required to determine whether episodes of acute kidney injury represent a risk factor for the development of chronic kidney disease.

Kidney-biopsy specimens from workers with established Mesoamerican nephropathy show chronic interstitial disease, tubular atrophy, inflammation, and interstitial fibrosis (Fig. S2 in the Supplementary Appendix). Glomeruli may be characterized by focal wrinkling of the glomerular basement membrane, a finding that is consistent with ischemia, and global glomerulosclerosis is common. Immune deposits and changes characteristic of diabetes have not been observed, and signs of hypertensive disease have been minimal or absent.[21,33,34]

At the time of diagnosis, the kidney disease is commonly advanced, at stage 3 or 4 (eGFR, 15 to 60 ml per minute per 1.73 m^2), with a subsequent decline in the eGFR of 3.8 to 4.4 ml per minute per 1.73 m^2 per year.[19,35] Although patients are initially asymptomatic, signs and symptoms of end-stage kidney disease (anemia, anorexia, nausea, and progressive uremia) develop in many patients over a period of several years, and unfortunately, adequate dialysis programs are not always available. Whether earlier identification of affected patients will make it feasible to reverse the disease is currently unknown.

SRI LANKAN NEPHROPATHY

A spate of chronic kidney disease of unknown origin has also been identified in the North Cen-

tral Province of Sri Lanka. The disease, which was first described in the 1990s, affects persons working in the rice paddies in rural regions.[36] Men are more commonly affected than women, with an average age at presentation of 40 to 50 years.[37] The similarities to Mesoamerican nephropathy are noteworthy, with most patients presenting with asymptomatic elevations of serum creatinine levels, low-grade or no proteinuria, and chronic interstitial nephritis with variable glomerulosclerosis in patients who undergo renal biopsy.[33,38-40] Other features observed in Mesoamerican nephropathy are also common in Sri Lankan nephropathy, including hyponatremia, hypokalemia, hypomagnesemia, and hyperuricemia. In some communities, up to 10% of the population is affected.[41] As in Mesoamerican nephropathy, patients with the disease may have acute kidney injury as an initial event.[42] Badurdeen et al. reported that some patients present with fever, leukocytosis, back pain, and arthralgias; urine specimens from such persons contain leukocytes and red cells despite minimal proteinuria, and renal biopsy shows an acute lymphocytic interstitial nephritis.[42]

UDDANAM NEPHROPATHY

Numerous cases of chronic kidney disease have been reported among rural farmers in India, especially in Central India in the states of Andhra Pradesh, Odisha, Chhattisgarh, and Maharashtra.[43-45] Known as Uddanam nephropathy (named after a village in Andhra Pradesh), chronic kidney disease in India was first noted in the 1990s,[46] as it was in Sri Lanka, and its prevalence has increased during the past two decades. The disease is seen in hot, rural areas where farmers grow coconuts, cashew nuts, or rice. Affected patients usually present with normal blood pressure, low-grade or no proteinuria, and a relatively bland urinary sediment with occasional red cells and leukocytes. Renal biopsy, when performed, shows chronic interstitial disease with variable glomerulosclerosis.[43] Table 1 compares the reported characteristics of the disease in Central America, Sri Lanka, and India.

OTHER REGIONS WITH HIGH RATES OF CHRONIC KIDNEY DISEASE OF UNKNOWN CAUSE

There are reports of high rates of chronic kidney disease in other hot regions of the world (e.g., among rural farmers in Tierra Blanca, Veracruz State, Mexico, where the major crops are sugarcane, cantaloupe, papaya, and rice).[47] Two reports suggest that the disease may also be present in southern Egypt and the Sudan.[48,49]

POSSIBLE CAUSES

The cause of the upsurge in chronic kidney disease remains unknown. A variety of possible causes are being investigated (Table 2). Since most reports involve cases in agricultural communities, initial concern focused on agrochemicals, especially the herbicide glyphosate. Some pesticides are nephrotoxic and could contaminate the water supply. Indeed, studies have shown that the prevalence of chronic kidney disease in Sri Lanka is highest in areas where there are shallow wells in which toxins might become concentrated.[37,50,51] An increased risk of chronic kidney disease was reported among Sri Lankan farmers with occupational exposure to glyphosate,[51] and glyphosate was found in the topsoil and lakes.[52] Contamination of water by glyphosate or other pesticides could explain why some evidence of kidney disease can occasionally be seen in persons not working in the fields, including women and children.[53] However, glyphosate levels in the Sri Lankan wells have been reported to be very low, a finding that contradicts this hypothesis.[52] Few studies of Mesoamerican nephropathy have adequately evaluated glyphosate exposure. Better assessment of exposure is needed before this compound and other pesticides can be ruled out as causes of the disease.[54]

Heavy metals, as well as some minerals, are known to cause kidney injury, and numerous cases of kidney disease associated with exposure to lead[55] and cadmium[56] have been reported, whereas evidence associated with arsenic is limited.[57] The rich volcanic soil in Central America contains many heavy metals, and cadmium and arsenic are also common in the soil of Sri Lanka. Cadmium toxicity was initially suspected in Sri Lanka, but more definitive studies could not confirm heavy metals as a causative agent for the unexplained increase in chronic kidney disease.[58] More recently, silica has been considered as a cause, especially in Central America and in India. Silica is commonly present in airborne material in burned sugarcane fields.[59] Silica is also present in high concentrations in wells in India where Uddanam nephropathy has been reported.[45] Respiratory exposure to silica has been associated with chronic kidney disease,[60] and silica admin-

Table 1. Demographic and Clinical Characteristics of Chronic Kidney Disease of Unknown Cause.*

Variable	Mesoamerican Nephropathy	Sri Lankan Nephropathy	Uddanam Nephropathy
Region	Pacific Coast, rural areas from Mexico to Panama	North Central Province	Central Indian states of Andhra Pradesh, Odisha, Chhattisgarh, Maharashtra
Demographic features	Age range, 20–50 yr Male:female ratio, ≥3:1	Age range, 40–50 yr Male:female ratio, 1.3:1	Age range, 30–60 yr More common in men
Affected population	Sugarcane workers, cotton workers, corn farmers, construction workers, port workers, miners, fishing industry workers, shrimp farm workers, brick workers	Rice farmers	Cashew, rice, and coconut farmers
Hypothesized causes			
Heat exposure	Low-altitude areas with hot tropical climate, physical exertion, recurrent dehydration	Low-altitude areas with hot tropical climate	Coast and inland up to 60–70 m above sea level with hot tropical climate
Other	Toxic causes: pesticides, heavy metals, NSAIDs, tobacco use Infections: leptospirosis, hantavirus infection Gene–environment interactions	Cadmium, pesticides (glyphosate), hard water, high fluoride content in drinking water, arsenic, glyphosate chelation with metals, low water intake, malaria	Silica in groundwater, excessive use of painkillers, low water intake
Clinical findings			
Acute phase	Fever, elevated serum creatinine level, muscle and joint pain, leukocytosis, leukocyturia, hematuria	Fever, fatigue, dysuria, joint pain, elevated serum creatinine level	Not described so far
Chronic phase	Insidious presentation (elevated serum creatinine level), low-grade or no proteinuria, hypokalemia, hyponatremia, hypomagnesemia, frequent hyperuricemia, reduced kidney size on ultrasound	Insidious presentation (elevated serum creatinine level), low-grade or no proteinuria, hypokalemia, hyponatremia, hypomagnesemia, frequent hyperuricemia, reduced kidney size on ultrasound	Insidious presentation (elevated serum creatinine level), low-grade or no hypertension, low-grade or no proteinuria, microscopic hematuria (rare), reduced kidney size on ultrasound

* NSAIDs denotes nonsteroidal antiinflammatory drugs.

istration causes chronic interstitial nephritis in experimental animal models.[61]

Other potential causes of chronic kidney disease include infectious diseases that can lead to tubulointerstitial injury, such as leptospirosis and hantavirus infection. Leptospirosis is common in sugarcane workers and may lead to chronic kidney disease.[62] However, to date there is little support for these infections as causative.[63] Likewise, although contamination of crops with aristolochia, a nephrotoxic herb, was a cause of an endemic chronic kidney disease in the Balkans,[64] there is no evidence supporting a role for aristolochia in the current regions in which the disease is endemic. Among agricultural workers from these regions, tobacco smoking[16,58] and use of nonsteroidal antiinflammatory drugs (NSAIDs)[16,20] have also been identified as risk factors for acute kidney injury, but neither can be viewed as the primary etiologic risk factor for chronic kidney disease.

Genetic factors may also be important and could account for familial clustering of this condition in communities.[22,65] Genetic variants may also explain why kidney disease develops in some but not all persons in at-risk workforces and why renal function has improved in some workers but declined in others during the harvest season.[16] Indeed, initial studies identified polymorphisms in SLC13A3 (sodium-dependent dicarboxylate transporter member 3)[58] and KCNA10 (a voltage-gated potassium channel)[66] that were associated with Sri Lankan nephropathy. This observation will require validation in additional studies.

One striking finding is that the regions in which chronic kidney disease has been reported tend to be the hottest regions in the various countries.[47] In line with this finding is the observation that chronic kidney disease among sugarcane workers is more likely to develop in those who work at sea level than in those who work in sugarcane fields at higher altitude, since the fields at low altitude have higher environ-

Table 2. Hypothesized Occupational and Environmental Risk Factors for the Development or Progression of Chronic Kidney Disease (CKD).

Possible Cause	Potential Mechanisms	Positive Evidence	Negative Evidence
Heat and dehydration	Repeated intermittent injury from four processes: Heat stroke (elevated body temperature) with inflammatory response Dehydration leading to hyperosmolarity, mediated by vasopressin and polyol pathway Heat exposure and exertion, leading to repeated subclinical rhabdomyolysis Increased core temperature, leading to uricosuria or crystalluria	Heat and dehydration cause CKD in animals CKD occurs in hot regions, and symptoms of dehydration are common Acute kidney injury correlates with heat exposure and physical exertion Heat stroke may cause acute kidney injury with late chronic interstitial nephritis Hyperuricemia and urate crystalluria are common in sugarcane cutters	There is limited evidence that acute kidney injury during a work shift leads to CKD CKD has not been reported in some extremely hot regions of the world Many occupations associated with heat exposure have not been associated with an increased risk of CKD No studies have shown that preventing acute kidney injury with hydration reduces the risk of CKD Hyperuricemia is not required for CKD to develop
Pesticides: glyphosate, paraquat, 2,4-dichlorophenoxyacetic acid, atrazine, cypermethrin, organophosphates, carbamates	Uptake from urine into the proximal tubule of the kidney, with toxic effects	Pesticides are commonly used in agriculture, and some are known to be nephrotoxic; they can get into soil, crops, and groundwater The increase in Sri Lankan nephropathy in the 1990s corresponded with increasing mechanization and use of pesticides	Most studies show minimal levels of pesticides in the drinking water in affected regions No obvious signs of pesticide intoxication have been reported in association with CKD Pesticides comprise hundreds of active ingredients, and pesticide use is heterogeneous across regions and crops Besides glyphosate, no potential etiologic agent has been identified CKD has not been reported in many regions with extensive use of glyphosate or other pesticides
Heavy metals, minerals, and halides: arsenic, cadmium, lead, silica, fluoride, other (magnesium, mercury, nickel, uranium)	Uptake from urine into the proximal tubule of the kidney, with toxic effects	Many metals have known toxic effects on the kidney Silica levels are high in wells in areas affected by Uddanam nephropathy, and silica is also present in sugarcane soot and air particles; silica can cause chronic interstitial nephritis in animals	Most studies have not shown elevated concentrations of heavy metals or fluoride in groundwater; patients with CKD do not have silicosis of the lung
Infections: leptospirosis, hantavirus infection, vector-transmitted diseases (malaria, dengue)	Leptospirosis and hantavirus infection can cause acute kidney injury, leptospirosis can cause acute interstitial nephritis and fever, and malaria and dengue can cause acute kidney injury	Leptospirosis is common in rural agricultural workers, as are malaria and dengue; chronic infection from leptospirosis can lead to chronic interstitial nephritis	There is no evidence that leptospirosis or other infections are more common in patients with CKD than in those without CKD
Other: NSAIDs, tobacco smoking, sugared and phosphate-containing drinks (fructose and phosphate), alcohol (illegal alcohol), aristolochic acid, herbal remedies	Most of these are known risk factors for acute kidney disease or CKD	Some of these have been reported to be risk factors for Mesoamerican and Sri Lankan nephropathy (especially NSAIDs and tobacco)	Many persons in these regions in whom CKD develops do not have a history of NSAID or tobacco use

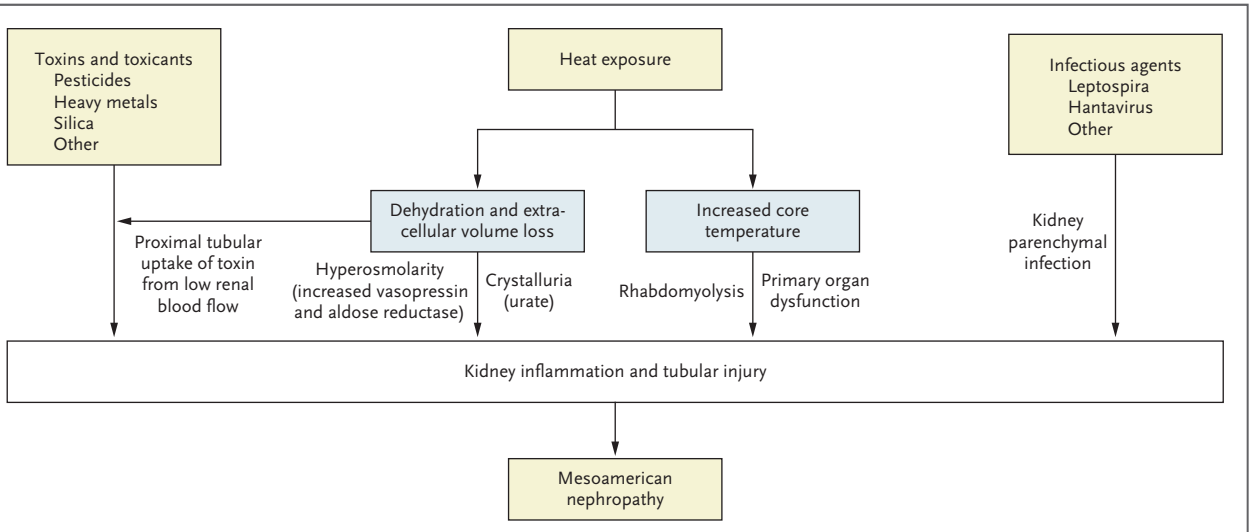

Figure 1. Possible Mechanisms for the Development of Mesoamerican Nephropathy.

One possible mechanism that has been proposed for the development of Mesoamerican nephropathy is the uptake of toxins in the tubules, resulting in direct toxicity. Another proposed mechanism is heat exposure leading to dehydration and volume depletion or an increase in core temperature, which may cause kidney injury directly through tissue dysfunction or indirectly through hyperosmolarity or rhabdomyolysis. In addition, heat-associated dehydration may also cause kidney injury by amplifying the renal effects of toxins or toxicants. It has also been proposed that infectious agents may be involved in the pathogenesis of Mesoamerican nephropathy, although this hypothesis remains unproven. For all mechanisms, genetic factors could be important.

mental heat.[5,15,16,67] Sugarcane workers often work with limited shade at environmental heat levels that generally exceed recommended limits for physical activity,[68] and many of these workers have symptoms of heat stress and dehydration.[67,69,70] Workers with abnormal kidney function who are exposed to severe conditions are at risk for job loss and reduced productivity.[71] A study in Sri Lanka showed that prolonged sun exposure and low fluid intake were risk factors for the development of chronic kidney disease.[72]

Several mechanisms that might result in chronic kidney disease from prolonged, physically demanding work in hot environments have been suggested (Fig. 1). For example, heat stress and dehydration could potentiate toxin-mediated kidney injury by enhancing reabsorption of toxins in the context of volume contraction.[40] Also, heat stroke is known to cause acute kidney injury, with fevers, leukocytosis, and leukocyturia, as well as hypokalemia, hyponatremia or hypernatremia, and hyperuricemia.[73-76] Kidney-biopsy specimens from affected persons show acute interstitial nephritis and tubular injury, and some of these patients subsequently have chronic interstitial disease.[75,77] It is possible that the symptomatic acute kidney injury observed is a type of mild heat stroke and that milder forms of heat illness may be subclinical. The kidney is sensitive to heat stress, and low-grade injury can occur with modest heat exposure, especially when combined with physical exertion.[78] Other effects of heat stress, physical exertion, and dehydration that may be mechanisms for acute or chronic kidney injury include clinical or subclinical rhabdomyolysis,[16,24] elevation in the serum urate level and urate crystalluria,[74,79] release of vasopressin, and activation of aldose reductase in the kidney, with aldose reductase generating oxidative stress.[80,81]

Those who believe that heat stress plays an important part in chronic kidney disease have suggested that the increase in prevalence may be due to climate change with even higher temperatures, suggesting that this disease may become more common over time. Acute kidney injury associated with manual labor and heat has recently been reported in Florida and California,[82,83] but documentation of an associated increase in rates of chronic kidney disease is lacking. A limitation of the heat-stress hypothesis is the fact that there are many hot regions in the world where this type of kidney disease is uncommon or has not been reported.[84] For example, few cases have been reported in the northern tip of Sri Lanka, even though this area is as hot as the regions with the highest frequency of disease. Although

this observation poses a challenge to the heat-stress hypothesis, it may reflect a lack of careful study of this region (ascertainment bias) or regional differences in prevailing labor conditions.

PREVENTION AND TREATMENT

PREVENTION

Because chronic kidney disease is largely an occupational and environmental health problem, primary and secondary prevention strategies have focused on preventing heat-associated health risks, mitigating nephrotoxin exposures, and conducting medical surveillance in at-risk populations to identify illness at subclinical and clinical stages.

In Central America, most preventive policies and actions have been focused on reducing heat and sun exposure and improving hydration with safe water and electrolytes.[16,26,67,85] When Mesoamerican nephropathy was first recognized, sugarcane workers had an average water intake of only 5 to 6 liters during a work shift.[25,69] Dehydration was common, and in one study, 187 sugarcane workers had a mean loss of 2.6 kg of body weight during a work shift, which was associated with a mean rise in the serum creatinine level of 0.3 mg per deciliter (27 μmol per liter).[25] In 216 workers who were told to drink 10 liters of water daily with two electrolyte packages, weight during the work shift was maintained, and the serum creatinine level increased by only 0.1 mg per deciliter (9 μmol per liter).[25,27] More recently, the Worker Health and Efficiency Program implemented a hydration and shade intervention, including the provision of tents for shade, refillable water containers, an increased number of breaks, and other preventive measures, which tended to slow the reduction in the eGFR during the harvest (from −5.3 to −3.4 ml per minute per 1.73 m^2), although the difference was not significant.[26,67] A recent study in Guatemala also showed that adherence to recommendations of higher water intake, rest, and shade reduces but does not eliminate the risk of acute kidney injury.[16,27] These studies suggest that hydration, together with rest and shade, is important but probably not fully sufficient to prevent short-term or acute kidney injury in all workers, especially those with the highest physical work demands. There is still no proof that improved hydration can slow the development of chronic kidney disease.

Preventive efforts in Sri Lanka have focused on obtaining safe drinking water and eliminating potential nephrotoxins in the environment. Such efforts include a government ban on glyphosate and four other nephrotoxic pesticides that was introduced in 2015 (although glyphosate has been allowed with some restriction since 2018). Also in El Salvador, there was political action against pesticides to address chronic kidney disease. In 2013, the Congress of El Salvador approved the prohibition of 53 pesticides, including nephrotoxic paraquat and glyphosate; however, the ban was never enacted into law.

CLINICAL MANAGEMENT

As noted above, persons presenting with chronic kidney disease of unknown origin often have normal blood pressure, normal blood sugar levels, and no other known medical illness. Clinical evaluation consists of monitoring the rate of decline in the eGFR. Kidney biopsy may be useful to confirm the disease. Laboratory tests include urinalysis and measurement of serum creatinine, sodium, potassium, magnesium, uric acid, and creatine kinase levels. A detailed occupational and environmental history taking is recommended to identify a history of physically demanding labor in a hot environment, infectious disease such as malaria or leptospirosis, or use of potentially nephrotoxic agents such as tobacco, NSAIDs, herbal supplements, and pesticides at home or at work.[86] If a person is working in a high-risk industry, temporary or permanent restrictions from performing heavy labor in hot environments may be recommended. Treatment is supportive. Patients in whom nephropathy progresses to end-stage kidney disease will require dialysis or transplantation, although these treatments are not always available. In low-resource communities with high incidence rates, attempts to find ways to provide access to peritoneal dialysis or hemodialysis have been increasing. Because of the tendency toward volume depletion, renin–angiotensin inhibitors should be used cautiously; there is no firm evidence of their benefit. There has been interest in the role of uric acid, since hyperuricemia is common in affected patients[12,22] and because experimental studies suggest that allopurinol may provide protection against heat stress–induced renal injury.[87] Clinical trials will need to be performed to determine whether lowering uric acid levels is beneficial.

FUTURE STEPS

Case definitions and characterization of chronic kidney disease in various regions of the world should be improved to facilitate comparisons among them. A standardized approach has been suggested for prevalence studies internationally, particularly in low- and middle-income populations, with some adjustments for the specific locality (DEGREE [Disadvantaged Populations eGFR Epidemiology Study] protocol),[88] which should develop into longitudinal efforts and include populations of workers at high risk. The role, if any, of acute changes in kidney function during a work shift as a predictor of chronic kidney disease requires further investigation. Large-scale occupational health surveillance programs are needed in high-risk regions and industries for improved detection, referral, and clinical treatment. A better understanding of etiologic factors requires improved measurement of all the proposed factors in populations tracked over multiple years. Such efforts may identify hot spots warranting intensified efforts in education, research, and prevention.

Despite the uncertainty about etiologic factors, governments and high-risk industries can design and implement interventions, especially those addressing heat stress and toxic exposures, under the precautionary principle.[89] Implementing measures that ensure hydration, rest, and shade for workers is good occupational health practice that can reduce the risk of heat stroke and dehydration while improving work efficiency,[67] but determining whether such measures reduce the incidence of chronic kidney disease requires strong longitudinal study designs. When clinicians identify clusters of patients with chronic kidney disease who work for the same employer or in similar jobs, they should contact occupational health authorities to ask them to investigate workplace conditions and pursue mitigation of risks by applying the hierarchy of controls where possible (www.cdc.gov/niosh/topics/hierarchy/default.html). Workplace screening programs are already in place in some large sugarcane companies in Central America, and such efforts should be extended to other high-risk work sites and industries. Medical follow-up care is very inconsistent in resource-poor areas where chronic kidney disease is endemic, and this problem must be addressed urgently.

SUMMARY

A spate of chronic kidney disease is occurring in several regions of the world, affecting manual workers in hot, agricultural communities. The causes remain unclear but may involve a complex interplay of environmental exposures, infections, genetic factors, and heat. Preventive measures have included programs to ensure safe drinking water, adequate hydration, rest, and shade for workers at risk, as well as to reduce exposure to toxins. However, proof that these interventions are reducing the incidence of chronic kidney disease has yet to be provided. International collaborative research efforts would help accelerate the search for causes and provide adequate prevention and treatment in resource-poor countries with little or no access to renal-replacement therapy.

Dr. Johnson reports holding equity in XORTX Therapeutics and Colorado Research Partners and holding patent no. 8,557,831 (on compositions and methods for treatment and prevention of insulin resistance, licensed to XORTX), patent no. 9,155,740 B (on compositions and methods for treatment and prevention of hyperuricemia-related health consequences, licensed to XORTX), patent no. 9,387,245 (on methods and compositions for the inhibition of fructokinase), pending patent no. 14/3051876 (on plant-based inhibitors of ketohexokinase for the support of weight management), and pending patent no. WO2018-170517 (on indazole inhibitors of fructokinase [KHK] and methods of use in treating KHK-mediated disorders or diseases); and Dr. Newman, receiving grant support and access to workforce and local infrastructure, provided to the University of Colorado, from Pantaleon. No other potential conflict of interest relevant to this article was reported.

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