Mesoamerican Nephropathy

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Summary: Mesoamerican endemic nephropathy is a type of chronic kidney disease of unknown origin, present in pockets of high prevalence along the Pacific Ocean coast of the Mesoamerican region, from southwest Mexico to Costa Rica. The disease is common in young adult men, most often yet not exclusively from agricultural communities, and with a high mortality rate. Kidney biopsy specimens show primarily tubular atrophy and interstitial fibrosis with some glomerular changes attributed to ischemia. Exposure to agrochemicals, heavy metals or metalloids, intense physical activity under heat stress with dehydration, infections, among other possible causes have been hypothesized as the culprit of the disease. Hypokalemia and hyperuricemia are frequent clinical features. Early diagnosis is key to initiate timely treatment and slow down the progression to end-stage kidney disease. At present, our knowledge about the magnitude of the disease burden imposed by Mesoamerican endemic nephropathy is clearly incomplete and its cause has not been determined. There is a need to implement epidemiologic and mechanistic research projects as well as formal chronic kidney disease and end-stage kidney disease registries in the Mesoamerican region to better understand the real extent of the epidemic, delimit risk populations, and to construct sound public health policy decisions.

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Chronic kidney disease (CKD) is the final common pathway of a diversity of renal conditions, some of primary renal origin (inherited nephropathies, primary glomerulopathies, among others) as well as systemic diseases (diabetes mellitus, essential hypertension, lupus erythematosus, vasculitis, and so forth). Mesoamerica, a region that comprises Southeast Mexico, Guatemala, El Salvador, Western Nicaragua, and Northwestern Costa Rica, has a significant burden of CKD from a diversity of known causes, including diabetes mellitus, which, as in other areas of the world, constitutes a major burden. In addition to the burden imposed by these causes of CKD, the region has witnessed along the past 2 decades the emergence of a major epidemic of CKD of unknown origin (CKDu), which has been named Mesoamerican endemic nephropathy (MeN) (Fig. 1). This condition constitutes a highly significant regional public health problem and has drawn the attention of local and regional health authorities as well as of worldwide organizations and researchers who are interested in understanding the cause and magnitude of this problem to be able to reduce its burden.[1,2]

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Since the emergence of nephrology as a subspecialty of medicine in the 20th century, localized pockets of high prevalence of CKDu have captured the attention of the discipline. It took the nephrology community nearly half a century to disentangle the most striking example of such endemic nephropathies: the Balkan endemic nephropathy, later renamed as *aristolochic acid nephropathy,* when the likely cause was identified.[3] In a similar way to what happened in the Balkan region, Mesoamerica has witnessed the presence of this unexplained and highly lethal nephropathy that progresses to CKD.[1,2] During these years, this epidemic has presented with continuous growth of incidence and prevalence, and those affected are mostly young male individuals who in the majority of instances progress undiagnosed to advanced CKD or even end-stage kidney disease (ESKD). Countries where this entity is present are low- and middle-income nations that have neither formal ESKD registries nor adequate infrastructure or a sufficient number of nephrologists, hence making the diagnosis of cases and the collection of proper epidemiologic data difficult.[2–4] Data available in relation to this disease come from a limited number of publications performed by a few groups of investigators, verbal communications, and hospital charts of affected individuals. At present, our knowledge about the magnitude of the burden of disease imposed by this condition is clearly incomplete, however, the available data show that in some countries, in particular El Salvador and Nicaragua, MeN constitutes the most common causes of premature death among young adult males.[5–7]

MeN presents in specific hotspots, most often located in rural agricultural communities, however, it also has been described in areas with other economic activities such as fishing and mining. What all of these hotspots have in common is their location in coastal lowland areas with

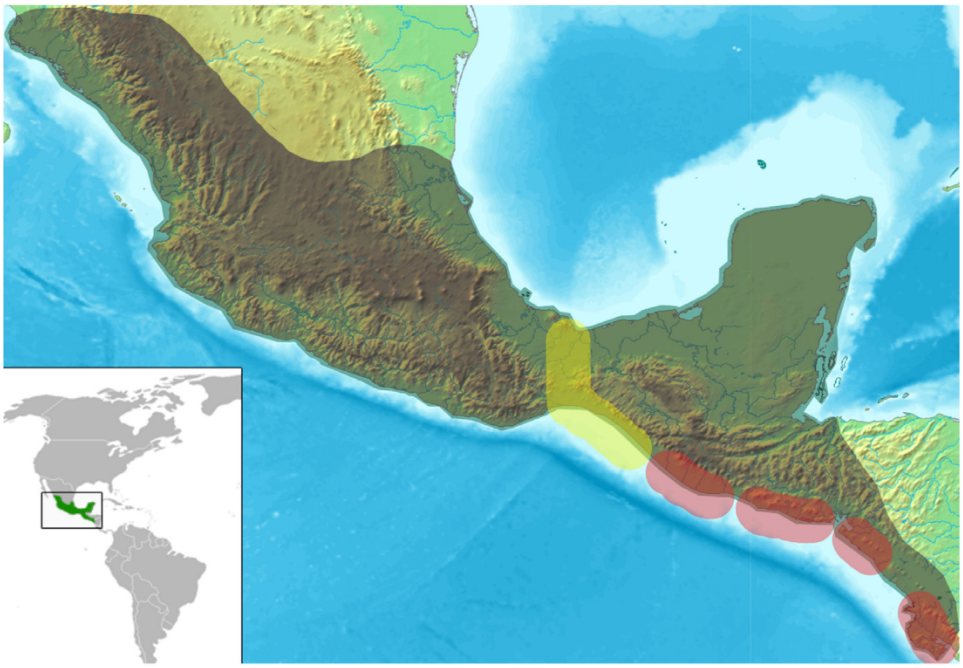

Figure 1. The Mesoamerican region (shadowed). Confirmed (red) and suspected (yellow) hotspots of Mesoamerican endemic nephropathy. Map image source: Wikimedia Commons. Available from: https://commons.wikimedia.org/wiki/File:Mesoam%C3%A9rica_relief_map_with_continental_scale.png.

high humidity and very high ambient temperatures, and that their inhabitants are people of Hispanic mestizo ethnicity, which is a combination of Native American and Caucasian.

The exact starting point of the epidemic is unknown because of the absence of reliable records and lack of nephrology services because they only started to develop in the main cities of the region around the 1970s. The first formal description of an excess of CKD patients with a distinct clinical picture pointing toward the identification of a new clinicopathologic entity was brought forward by García-Trabanino et al[8] and goes back to the end of the past century in a referral hospital from El Salvador. Nevertheless, mortality trends resulting from CKD in Costa Rica show a clear pattern, with a predominance of young males in the Pacific Ocean coastal regions since at least the 1970s.[9] This, and personal communications from colleagues from Mesoamerica, suggest that the disease may have been present before the first formal publication and its precise time emergence is unknown, given that in the 1970s and 1980s the access to health and practicing nephrologists were both extremely scarce in the region. After the first report in 2002, several studies consistently confirmed the continued presence of CKDu cases following the same epidemiologic profile and clinical picture, in particular in Nicaragua, Costa Rica, Guatemala, and again in El Salvador.[10–13]

A significant fact that needs to be highlighted is that MeN is imposing an extra burden of disease on top of the usual burden of diabetic and hypertensive patients, to the point that it has pushed the mortality rates of CKD of some of the Mesoamerican region countries to epidemic levels, with Nicaragua and El Salvador ranking among the top countries with high CKD mortality rates worldwide, which are comprised mostly of young adult males with premature death.[2,14,15]

EPIDEMIOLOGY

After more than a decade of systematic work by a diversity of health professionals (epidemiologists, clinicians, toxicologists, and public health professionals, among others) and two international research workshops that were coordinated by the Consortium for the Epidemic of Nephropathy in Central America and Mexico, we now have a case definition and description of the disease that is accepted by most groups.[16] In addition, a combined effort established by the Latin American Society of Nephrology and Hypertension in collaboration with the Pan-American Health Organization culminated in a publication that reported a definition for surveillance.[17] As stated previously, MeN does not follow the expected patterns of known causes of CKD.[1,5,6,16,17]

The classic MeN patient is a Hispanic, 20- to 60-year-old man living or working on the Pacific coastlands of Central America.[4] In a study performed in Chichigalpa, Nicaragua, nearly 40% of 20- to 40-year-old male participants had an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2.[18] In the Bajo Lempa region, El Salvador, the average annual incidence rate of ESKD was 1,409[8] per million population, 89% of the affected

individuals were male, and the mean annual mortality rate was 128 per 100,000 population.[15] In contrast, the average ESKD incidence rate in Latin American is 190.8 per million population, and the average annual mortality rate in most Latin American countries rarely surpasses 10 per 100,000 population.[14] The male predominance in ESKD incidence and mortality increased markedly when diabetic and hypertensive patients are excluded, strikingly up to 97% in the Bajo Lempa region.[1,2,9,14,15]

Because the coastal regions are predominantly agricultural, most MeN patients perform agriculture-related chores. According to community and hospital-based reports, 70% to 80% of affected individuals in CKD hotspots are farmers and the rest work in other occupations.[8,10,13,15,19–21] However, the most studied population has been the sugarcane cutters, possibly because sugarcane cutting is among the most strenuous occupations, its ubiquity in the Chichigalpa region, and its social implications.[22]

Some studies also have described the presence of markers of kidney damage, including data suggesting hyperfiltration or altered kidney function not attributable to diabetes or hypertension in women and children from the affected regions or in populations living at higher altitudes away from the coastal hotspots, however, the incidence, prevalence, and mortality rates resulting from CKD, as well as the presence of ESKD, are not increased or are only slightly increased in these populations.[15,23–26]

CLINICAL FINDINGS

Because MeN is a recently identified clinical entity and given that most patients seek medical assistance only after ESKD ensues, the clinical manifestations of MeN have remained blurred for many years and the disease often has been described as asymptomatic. With time and increasing efforts for early diagnosis, the clinical picture of MeN now is better understood and some patterns have emerged. A recent report showed a likely initial presentation of MeN as an acute kidney injury (AKI) clinical syndrome accompanied by an acute systemic inflammatory response. Nondiabetic and nonhypertensive, seemingly previously healthy, workers from a known hotspot of MeN were described as presenting with an increased serum creatinine level that would fulfill the criteria of AKI plus leukocyturia, and at least two of the following clinical manifestations: fever, nausea or vomiting, back pain, muscle weakness, headache, or leukocytosis and/or neutrophilia. Remarkably, 8.5% of these patients progressed rapidly to CKD after the acute onset in a median of 3 months.[27,28]

As previously discussed, those affected were diagnosed most often with established moderately advanced stages of CKD. Patients usually were discovered incidentally to have a significantly increased serum creatinine level and only more recently in earlier stages through community early diagnosis campaigns. On close questioning, patients often described a history of muscle weakness, which likely was associated with hypokalemia events, a laboratory manifestation often associated with this disease. In addition, they also often described what could be referred to as aseptic dysuria, possibly associated with significant dehydration and the passage of sandy urine or crystals in urine.[29,30] Blood pressure usually was normal or in the lower range, and peripheral edema was rare.

At advanced stages of CKD, the clinical characteristics are similar to those observed in most other causes of CKD and ESKD, although the presentation may be similar to other tubulointerstitial diseases in that the patients usually are normotensive or only slightly hypertensive.[8,13,31–34] In these regions, there also is frequent use of nonsteroidal anti-inflammatory drugs as painkillers, self-prescribed antibiotics, and herbal remedies (either self-prescribed or prescribed by general practitioners or even nonphysicians).[21,35]

When reviewing laboratory and imaging studies, in addition to the presence of increased serum creatinine and blood urea nitrogen, hypokalemia and hyperuricemia frequently are described as well as the presence of abundant urate crystals in urinalysis. Proteinuria generally is absent or only mild (A1 or A2 Kidney Disease Improving Global Outcomes categories). Later in the course of the disease, hyponatremia also is common. A few studies have reported an increase in biomarkers of acute tubular injury, including NAG (N-Acetyl-β-D Glucosaminidase), interleukin 18, and NGAL (Neutrophil gelatinase-associated lipocalin).[19,24,31–33,36] Few reports are available on imaging studies, with kidney ultrasound showing nonspecific features, including small kidneys and loss of the corticomedullary relation in advanced stages of CKD.[37] In early stages of CKD, an ultrasound usually shows normal-sized kidneys with increased echogenicity (Table 1).

When diagnosed timely, patients seem to respond well to oral bicarbonate supplements and allopurinol to normalize serum uric acid and reduce urate crystal excretion, if given in combination with proper hydration recommendations. In a recent study, allopurinol lowered serum uric acid, reduced kidney fibrosis, and improved renal function in heat-stressed mice,[31,38] and, interestingly enough, this prescription seemed to improve the dysuria often referred to by MeN patients after a strenuous workday under the sun, which is not improved by the implementation of proper hydration and rest breaks under shade only (personal observation by García-Trabanino).

HISTOPATHOLOGY

Few studies have described the findings of kidney histopathology of MeN patients from El Salvador and

Nicaragua, however, their findings are largely consistent. Recently, a study describing kidney biopsy specimens from a hotspot in Nicaragua on apparently previously healthy patients presenting with clinical manifestations of AKI showed tubulointerstitial nephritis with varying degrees of inflammation and chronicity, with mostly preserved glomeruli, no immune deposits, and few mild ischemic changes. These clinical manifestations and kidney histology lesions could well be describing the onset of the disease.[27,28]

Three multinational groups working in El Salvador and Nicaragua have published data obtained from kidney biopsy specimens in patients with MeN. All of these studies consistently reported tubular atrophy and interstitial fibrosis in association with a variety of glomerular changes. Thickening of Bowman's capsule in conjunction with shrinking of glomerular capillaries suggest renal ischemia. In addition, vascular lesions are very uncommon. There is an absence of mesangial proliferation, and no immune complex deposits of any nature. These findings point to a primary tubulointerstitial disease, and although there is some degree of glomerular involvement, and often global glomerulosclerosis, these changes may occur in any advanced form of CKD.[34,39,40] Another recent study compared kidney samples from Sri Lanka, where a similar endemic nephropathy also is present, with those of MeN patients from El Salvador and Nicaragua. When compared with the results from the Mesoamerican region, the morphology observed in the samples from Sri Lanka was more heterogeneous, and interstitial inflammation and vascular changes were more common. Remarkably, the biopsy specimens from two patients showed morphologic signs of acute pyelonephritis, but with negative urine cultures. In accordance with MeN, patients from Sri Lanka also presented with hyponatremia, hypokalemia, and other electrolyte disturbances, and albuminuria was infrequent or mild. The investigators concluded that there were many similarities in the biochemical and morphologic profile of both endemic nephropathies but, nevertheless, there were differences too, such as the mixed morphology and the more marked interstitial inflammation and vascular changes in the Sri Lankan samples.[41]

POTENTIAL RISK FACTORS AND CAUSES OF MEN

At present, the cause of MeN still is unknown, although some progress has been made over the past years. Despite this progress, it is critical to underscore the need for a more comprehensive research effort, appropriately financed, to make significant progress in better understanding of the etiology and therapeutic interventions for MeN.

Given some similarities between MeN and other CKDu disease seen in other geographic regions, there continues to be a debate as to whether or not the CKDu in Mesoamerica is the same disease, as that observed, for example, in Sri Lanka and the Andhra Pradesh region in India.[42,43] Although there were significant similarities, specifically the findings of substantial tubulointerstitial disease, at the current time there are not enough data to confirm or refute the fact that there is some common precipitant or genetic factors that would account for the similarities. Appreciating similarities and differences in the conditions is the focus of ongoing research efforts.

To date, some of the most important risk factors proposed as possibly related to the appearance of MeN are as follows: (1) exposure to one or more pesticides or agrochemicals; (2) exposure to heavy metals or metalloids; (3) recurrent dehydration episodes in association with extremely harsh physical work, as happens with sugarcane cutters, performed in very humid and hot climates; (4) infectious agents such as *Leptospira* or hantavirus; and (5) other factors, including concomitant use of nonsteroidal anti-inflammatory drugs as well as herbal remedies, or the frequent intake of sweetened beverages. A common shared condition noted in all publications and clinical observations was the preponderance of poverty and social deprivation in those affected around the globe.[1] Given what is known about the natural history of the disease, the complexity and diversity of potential risk factors, this is likely a multifactorial or multiple-hit factor condition (Table 2).

Agrochemicals

Synthetic fertilizers and pesticides are used extensively in agriculture in the Mesoamerican region to control pests and prevent crop yield losses or product damage, however, they often are toxic to human health and are without a doubt a major concern for those dedicated to agricultural activities as well as for research groups and public health systems.[44] Multiple pesticides clearly have shown to condition acute as well as chronic toxicities, most often neurologic, oncogenic, respiratory, hepatic, fertility−related, and other.

The use of agrochemicals is quite extensive in all of Mesoamerica as well as in other countries that face epidemics that have similarities, such as Sri Lanka and the Andhra Pradesh region in India. In addition, some of the products that are in use and are used commonly in these parts of the world already have been banned in some developed nations. This hypothesis is strongly supported by the fact that the geographic distribution of the disease is mainly in agricultural communities, however, the presence of affected individuals in nonagricultural communities, such as mining or fishing communities, strongly questions its strength.[19] In northern Sri Lanka, a form of CKDu present in rural communities has been strongly linked to exposure to pesticides, as well as to heavy metals or metalloids.[42,45] In the Mesoamerican

Table 1. Mesoamerican Nephropathy: Clinical Manifestations

	Symptoms	Signs	Laboratory Findings	Ultrasound
CKD			GFR normal or low	
	Nearly asymptomatic	BP normal or low range	Albuminuria A1-2 KDIGO	Increased echogenicity
	Aseptic dysuria	Altered tendon reflexes*	Normal hemoglobin level	Normal or slightly reduced kidney size
	Muscle weakness*		Hypokalemia	
	Cramps*		Hyponatremia	
			Hypomagnesemia	
			Hyperuricemia	
			Urate crystals in urine	
ESKD	Severe uremic symptoms	Uremic signs	Albuminuria A1-2 KDIGO	Small kidney size
	Asthenia	Low, normal, or high BP	High creatinine and BUN	Increased echogenicity
	Cramps*	Paleness	Metabolic acidosis	
	Weakness	Mild or no edema	Marked anemia	
	Weight loss		Hypokalemia or hyperkalemia	
			Hyponatremia	

*Related to electrolytic disturbances.
Abbreviations: BP, blood pressure; BUN, blood urea nitrogen; GFR, glomerular filtration rate; KDIGO, Kidney Disease Improving Global Outcomes.

region, a study performed in El Salvador reported that agrochemicals are major players in the development of CKD, however, the odds ratio for development of CKD in that specific study was not increased in those exposed to pesticides.[21] A series of epidemiologic studies in the region and elsewhere have systematically linked agrochemicals with the risk of development of chronic kidney injury.[1,20,21]

Pesticide and synthetic fertilizer exposure has and should continue to be a major concern as a risk factor for induction of harm to human health, nevertheless, no specific pesticide or fertilizer has been pointed out with pathophysiologic or strong epidemiologic evidence as a clear causal agent conditioning the CKD epidemic, and no evidence-backed pathophysiological mechanisms have been described to date. Despite the insufficient evidence to link agrochemicals directly to MeN, we strongly support use limitations and, whenever possible, banning them from quotidian use.[44]

Heavy Metals

Heavy metals and metalloids (lead, cadmium, arsenic, and others) may constitute environmental toxins that are prevalent in some of the affected regions.[45,46] The volcanic soils of Central America are rich in cadmium and arsenic, nevertheless manifestations of cadmium-related nephropathy, including proteinuria, renal glycosuria, hypercalciuria, and defects of concentration and acidification, are not present in MeN. A study performed in Nicaragua by McClean et al[19] from Boston University did not show any increase in environmental arsenic concentration and therefore confirmed that exposure to this element is not likely related to the epidemic.

Investigators from Sri Lanka have reported that arsenic or cadmium, in conjunction with agrochemicals, could be participating in the nephrotoxicity and kidney disease observed, yet the strength of the evidence in terms of causality is questionable.[43,45]

Recurrent Dehydration

Most individuals who develop MeN have a history of extremely strenuous working conditions associated with excessive working hours, few rest days, and physical exertion in extreme heat and humidity, conditions that may favor heat stress events and recurrent dehydration. Sugarcane harvesters of the Pacific coast lowlands of Central America are heavily exposed to these conditions.[47] Although workers in other occupations with extreme heat exposure, such as miners, construction workers, and port workers, also may be at risk, it is agricultural work in lowlands that stands out in affected communities. Some studies have explored how the exposure of those working outdoors harvesting crops

Table 2. Mesoamerican Nephropathy: Proposed Causes

Pesticides	Glyphosate
	Paraquat
	Chlorpyrifos
	Cypermethrin
	2,4-D
Heavy metals and metalloids	Lead
	Arsenic
	Cadmium
	Silica
Environmental toxins	Aristolochic acid
Drugs	Painkillers, aminoglycosides
Metabolic causes	Hypokalemia
	Hyperuricemia
Genetic	Hereditary disorders
Infectious agents	Leptospira
	Hantavirus
Heat stress and dehydration	Recurrent heat stroke
	Subclinical rhabdomyolysis
	Dehydration + vasopressin stimulation
	Dehydration + tubular fructokinase
	Cyclic uricosuria and crystalluria

compares with what may be seen in controls working in air-conditioned areas. The former presents a diversity of physiologic differences, including increases in serum creatinine levels at the end of daily working shifts.[48]

The presence of dehydration has been clearly linked to the occurrence or episodes of AKI, however, experimentally we have shown that daily dehydration may cause chronic tubulointerstitial injury. Dehydration may cause renal injury via diminished renal perfusion, glomerular ischemia (manifested as glomerular shrinking), and increased serum osmolarity. The latter may stimulate an increase in the renal polyol (aldose reductase) pathway to convert glucose to sorbitol and fructose in the proximal tubule, which in turn are metabolized by fructokinase, generating an increased local oxidative stress status that may cause local tubular injury.[49] In addition, strenuous physical activity as a result of harsh working conditions and repeated dehydration may induce rhabdomyolysis, also resulting in kidney injury. It is plausible to speculate that recurrent dehydration also could be playing a role in the pathogenesis of other endemic nephropathies seen in countries such as Sri Lanka and India, among others. Recurrent dehydration may be working in conjunction with other nephrotoxic exposures, including exposure to potentially harmful agrochemicals and the recurrent use of nonsteroidal anti-inflammatory agents or other herbal remedies often used in these regions.

A common worldwide feature of most endemic nephropathies of undetermined origin is the ambient temperature increase and very significant exposure to heat while performing exhausting labor-related tasks. Indeed, most of them are located between the equator and the tropic of Capricorn. Global warming is hitting some areas of the world with the highest increase in temperature and the Pacific coast of Central America is one of them, with one of the highest temperatures in the world in the past 50 years. We recently proposed the term *heat stress nephropathy* as a climate change–related global epidemic that likely could encompass all of the endemic nephropathies occurring in some areas of the world.[50] The recurrent heat exposure with physical exertion and inadequate hydration could lead to CKD that is distinct from that caused by diabetes, hypertension, or glomerulonephritis.[50]

Infectious Diseases

It has been clearly shown that some infectious diseases such as leptospirosis, hantavirus, or malaria may induce AKI, however, no evidence is in place to confirm that they may induce CKD. Leptospirosis is highly prevalent in the lowlands of the Pacific coast of Central America and Riefkohl[51] hypothesized that this infection may be a co-factor in conjunction with other nephrotoxic agents in the genesis of CKD.

Other Potential Etiologies

Aristolochic acid is derived from Aristolochia, a plant responsible for Chinese herb nephropathy and Balkan endemic nephropathy. This plant is found in Central America and its potential use in herbal remedies and even contamination of food supplies could be a risk. Nevertheless, its participation in MeN is highly unlikely because aristolochic acid nephropathy has a different histologic pattern, including primary renal fibrosis and inflammation, not consistent with what is seen in MeN. In addition, urothelial tumors frequently described in aristolochic acid poisoning are not present in MeN patients.[52]

Agricultural workers of Mesoamerica who are exposed and affected with CKD often use or abuse nonsteroidal anti-inflammatories as pain killers after exhausting work and, given their known nephrotoxicity, they may be contributors to CKD development.[35] In Nicaragua, the unregulated consumption of a sugarcane-derived distilled and unfiltered product contaminated with heavy metals or metalloids has been proposed as a potential cause of CKD.[53]

Finally, as stated earlier, all potential causes and pathophysiological mechanisms discussed are within the context of a social and economic environment of poverty and deprivation, which also may be playing a major role in the genesis of this disease and, surely, in the high mortality rate of MeN.

PREVENTION AND TREATMENT

It is urgent to better understand the causality of MeN to establish successful early preventive and treatment measures. Based on the current causal hypotheses, the best prevention available to the inhabitants of the afflicted regions nowadays is the limitation of heat exposure, provision of adequate hydration, and rest in shaded areas at proper intervals. Although it may be beneficial to promote early morning hour work, before the temperature increases excessively, there is proof that sugarcane workers perform their chores over the Occupational Safety and Health Administration recommended limits of heat stress and this can happen as early as 9 am in the morning.[31,54] In addition to proper hydration practices, other important measures that may be of help could be improved sanitation, banning of potentially harmful agrochemicals, and limiting exposure to those that are in use by using proper protective equipment. Avoidance of nonsteroidal anti-inflammatory drugs is recommended of course. Finally, we have to state again that poverty and social margination are critical factors that need to be addressed to face this epidemic.

At present, although efforts are being made to increase the availability of modern ESKD treatment in some countries of Central America, renal replacement therapy,

namely dialysis and transplantation, is not available to most of those who require it because of insufficient financial and human resources. Therefore, MeN has become the most common cause of death of young male individuals working in sugarcane plantations in the lowlands of the Pacific coast, particularly in Nicaragua and El Salvador.[1,55,56] There is an urgent need to increase coverage and treatment of those already affected with availability of dialysis and kidney transplantation.

CONCLUSIONS

Today, the existence of MeN poses a challenge to the global nephrology community. The urgent burden of a condition with an extremely high mortality rate, owing to a lack of available renal replacement resources, which disproportionately impacts young men, and whose specific etiology is not yet understood, creates an important burning platform for health care workers and researchers alike. In the past 2 decades this major epidemic of CKD among the communities in the Pacific lowlands of Central America has been quite well identified and described. This new form of CKD is not related to hypertension, diabetes mellitus, or obesity, and to date there is still no conclusive evidence of a clearly defined etiologic factor. Recurrent dehydration related to occupational exposure to heat stress in conjunction with other risk factors such as frequent exposure to agrochemicals, heavy metals and metalloids, nonsteroidal anti-inflammatory drugs, infectious diseases, or other nephrotoxins may play contributing roles in the genesis of this disease. In addition, the poor economic, social, and labor environment are consistently present in the impoverished rural communities of this area of the world and may be playing a major role in the genesis and the devastating effects of this epidemic.

Besides the indispensable need for further research on the possible causes of MeN, the current empiric treatment protocols used by the local physicians also need to be tested and their efficacy measured with appropriately designed trials. Thus, funding for research urgently is required to advance scientific knowledge.

Finally, the countries in the Mesoamerican region need to implement official CKD and ESKD registries in the short term to better understand the real extent of the epidemic, delimit risk populations, and to make sound public health policy decisions.

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