

The Central American Epidemic of CKD

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Summary

Recent reports have described an apparent epidemic of CKD along the Pacific coast of Central America, such that CKD is a leading cause of death among working-age men in lower-altitude agricultural communities in this region. Given the limited availability of kidney replacement therapies in this region, CKD often is a terminal diagnosis, lending greater urgency to the identification of a modifiable cause. This article discusses the epidemiology of CKD in this region, reviews the clinical features of this CKD outbreak, discusses potential causes and the evidence supporting these hypotheses, and highlights the wider implications of this epidemic of CKD.

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Introduction

Six of us stood on a row of small boulders at one end of a dirt lot just outside Chichigalpa, an agricultural community in northwest Nicaragua, that provided us a view of the hundreds of local residents who had assembled to meet us. It was June of 2009, and we were there to investigate reports of an epidemic of CKD, the leading cause of death among men in this region of Nicaragua (95 deaths per 100,000 inhabitants and a 5:1 male predominance) (1,2). The day was typically Nicaraguan—hot and humid—and after the bright sunshine of the morning, the sky was darkening with an impending afternoon storm. The assembled residents, mostly poor current and former sugarcane workers, their families, or their widows, were hoping that we would explain why either they or their family members had CKD, a condition that they believed was related to their work at the local sugarcane producer. We had met with leaders in this community earlier in the day and now spoke with the rest of the community, answering questions the best way that we could. When the downpour came, we escaped to a dry van.

What brought us there that day and many times since that time was an unusual process in which representatives of both the workers and company had decided to cooperate in an effort to determine the causes of the epidemic. This process was facilitated by the Office of the Compliance Advisor/Ombudsman of the World Bank, which had responded to a complaint filed by a group of former sugarcane workers. In this complaint, the workers alleged that local work practices were associated with the regional epidemic of CKD. Our team had been selected by both the company and the workers to investigate the epidemic, and we were there to learn more.

That evening, we met with the leaders of the company accompanied by their medical staff, which included a full-time nephrologist who had been hired in recognition of the seriousness of CKD in this region. We heard many of the same stories that we had heard

from workers but of course, from an alternative perspective. We quickly began to understand the complexities of the situation. For example, beginning in 2000, the company instituted pre-employment medical examinations, which included serum creatinine measurement, urine dipstick testing, and BP assessment at the start of the harvest season. Individuals with serum creatinine levels persistently above 1.2 mg/dl (later revised to above 1.4 mg/dl) were not hired (3). From the company's perspective, strenuous work might lead to additional kidney damage in already vulnerable individuals, with more rapid progression of CKD. At the same time, sugar cultivation and harvesting is the major driver of the limited local economy (Figure 1), and there are few alternative sources of employment that would provide a source of income for workers and their families. The result was a difficult juxtaposition of the need for employment versus considerations of safety and health.

In a region where dialysis and kidney transplant are not widely available, CKD is considered a terminal diagnosis. The situation in northwest Nicaragua is extreme, with kidney disease being a potentially destabilizing force in a country that is the second poorest in the Western hemisphere (4). However, this syndrome seems to be more widespread than just in a small region in Nicaragua; a similarly high prevalence of CKD reported in El Salvador, where CKD is the number two cause of death in adult men (5). In the remainder of this article, we will discuss the wider regional epidemic of CKD, review the clinical features of this CKD outbreak, discuss potential causes, and highlight the wider implications of this epidemic of CKD.

Epidemiology and Manifestations of Central American CKD

Based on several unpublished and published prevalence studies, review of clinical charts, and discussions with local physicians, it seems that the regional

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Figure 1. | A sugarcane field in northwestern Nicaragua before harvest. Reprinted from Constantino Schillebeeckx (Photo CS, LLC), with permission.

epidemic of CKD has several distinguishing characteristics: (1) although the apparent excess of CKD seems to extend across Central America, it is concentrated along the lowland areas of the Pacific coast; (2) men seem to be disproportionately affected, with creatinine elevations often noted in the third or fourth decade of life; and (3) significant proteinuria is uncommon, with a clinical profile most consistent with nonglomerular disease resulting in small echogenic kidneys on ultrasound imaging (Table 1) (2,3, 6–14). Additionally, a symptom complex referred to as *chistata* is common among individuals in this region. *Chistata* is a colloquial term used to characterize a constellation of symptoms, including lower urinary tract discomfort and urinary urgency, that approximate the clinical term dysuria. The etiology of *chistata* remains uncertain, although it is unlikely infectious (3), and whether *chistata* is associated with CKD remains unknown. Overall, the regional epidemic of CKD remains insufficiently studied, with no direct ascertainment of kidney function or creatinine clearance and no kidney biopsies in individuals with early stages of CKD.

The limited published community- and population-based literature on the epidemic of CKD in this region has focused on the prevalence of reduced GFR by sex,

occupation, altitude, and location, with some mention of heat stress (Table 2). For example, in Quezalguaque, a relatively low-lying community in northwest Nicaragua where residents are predominantly engaged in agricultural work, the prevalence of estimated GFR (eGFR) below 60 ml/min per 1.73 m² was 20% among men and 8% among women; this difference was most notable among men between 30 and 42 years, with 13.4% of men having an eGFR below 60 ml/min per 1.73 m² (4.9% of these men had a GFR below 30 ml/min per 1.73 m²) versus 3.3% (0%) of women (11). Furthermore, residents who lived at an altitude of <500 m above sea level were almost two times as likely to have an eGFR below 60 ml/min per 1.73 m² compared with those individuals who lived at a higher altitude. The results also suggested a possible association with occupational factors, such as past work in cotton or sugarcane, or exposure to pesticides. In contrast, in an inland high-altitude (~1000 m above sea level) village near Matagalpa, Nicaragua, where the primary industry is coffee production, few, if any, individuals below 40 years old had an eGFR less than 60 ml/min per 1.73 m² (15). Although there was no statistically significant association between prior work in the sugar or cotton industries and low eGFR in the Quezalguaque study, relatively low numbers and survival bias may have limited the ability to appreciate a significant association. Taken in sum, these two studies suggest that altitude may be a critical factor; whether this factor reflects temperature variation, different environmental conditions and exposures, or different work and social practices cannot be determined from these studies.

Two other moderately sized surveys have explored this issue in greater detail. In the first study, Torres *et al.* (13) sampled 1096 residents between 20 and 60 years who were involved in different industries in northwest Nicaragua: mining/subsistence farming (100–300 m above sea level), banana/sugarcane production (100–300 m), fishing (0–100 m), services (0–100 m), and coffee production (200–675 m). The work by Torres *et al.* (13) noted that eGFR was less than 60 ml/min per 1.73 m² in 14% of men versus 3% of women and that lower eGFR was more common in the lower-altitude, high-work intensity regions, specifically those areas engaged in mining/subsistence farming and

Table 1. Clinical features associated with endemic Central American CKD

Epidemiology of CKD

- Men more commonly affected
- Common in third to fifth decade of life
- Not associated with diabetes or obesity
- More common at lower altitudes

Uncertain association

- High local prevalence of lower urinary tract symptoms among men (*chistata*) often accompanied by pyuria and positive leukocyte esterase

Kidney and urinary tract manifestations

- Minimal to moderate proteinuria
- Indolent and slowly progressive
- Ultrasound shows small echogenic kidneys

A very limited number of biopsies performed in individuals with advanced disease shows fibrosis

When present, urinary symptoms with pyuria and leukocyte esterase positivity are accompanied by negative urine culture (3)

Table 2. Regional community-based studies of CKD

Locale(s) Studied	Occupation ^a	N	Altitude ^b	Prevalence and Population	Risk Factors
Nicaragua: Quezalguaque, León (11)	Mostly agriculture	771	Mostly low	High prevalence of reduced eGFR: 20% of men with eGFR < 60 ml/min per 1.73 m ² versus 8% of women	Residence at lower altitude associated with lower eGFR
Nicaragua: Five communities (13), León, and Chinandega	Subsistence farming and mining	445	Low	13.4% of men ages 30–41 yr with low eGFR High prevalence of reduced eGFR, with 14% of men but only 3% of women with eGFR below 60	Abnormal creatinine levels not common in higher-altitude villages
	Banana/ sugar Fishing Services Coffee	384 216 177 92	Low Low Low High	Abnormal creatinine levels in 31% and 24% of male and female agricultural workers, respectively, at 100–300 m above sea level; not occurring at higher altitudes	Banana/sugarcane independently associated with higher creatinine in men and mining/subsistence farming independently associated in both men and women
Nicaragua: Matagalpa (15)	Coffee	267	Very high	Very low prevalence of reduced eGFR, with no individuals below 40 years old having reduced eGFR	
El Salvador: Five communities (12)	Sugar/ Sugar/ Sugar Coffee Urban services	129 159 120 124 132	Low Low High Very high High	High overall prevalence of reduced eGFR	Discrepant findings in sugar communities, with kidney disease common at low-altitude sugar communities but rare in the high-altitude sugar community; 18% of men had eGFR below 60 in low-altitude sugar communities versus 0%–2% of men in high-altitude sugar communities Women less affected than men (8% in low-altitude sugarcane versus 1%–3% in other communities) Proteinuria uncommon and low grade
El Salvador: Two communities (10), Jiquilisco, Usulután and Sesori, San Miguel	Agriculture	291 62	Low High	Study included men only Sampling pattern only tested serum creatinine in male coastline residents with 1+ or greater proteinuria	Dipstick proteinuria (1+ or greater) noted in 46% of men in low-altitude coastal communities versus 13% of men in high-altitude inland communities 37 of 80 men with laboratory measurements had creatinine ≥ 1.5 mg/dl; of these 37 men, 81% had 1+ proteinuria, and only 19% had 2+ or greater proteinuria
El Salvador: Bajo Lempa region (5)	Agriculture	775	Low	eGFR < 60 ml/min per 1.73 m ² in 17% of men versus 4% of women	Nonsteroidal anti-inflammatory drug use common Most affected individuals with neither diabetes nor hypertension

Table 2. (Continued)

Locale(s) Studied	Occupation ^a	N	Altitude ^b	Prevalence and Population	Risk Factors
Nicaragua: Nine communities (34), León, and Chinandega	Varied	997	Not stated in the article but likely varied elevations	Men only after too few cases found in women 12.4% of population with eGFR below 60	Agricultural field labor, consumption of iija (alcohol available in a form susceptible to contamination by toxins), and consumption of >5 L water/d independently associated with the presence of reduced eGFR Hypertension and diabetes not more common in CKD

eGFR, estimated GFR.
^aSugarcane cutting is considered the most intensive in terms of physical labor, and services jobs are considered the least physically intensive.
^bTemperatures are significantly lower at higher altitudes; low altitude suggests elevations from sea level to 100 m, high altitude suggests elevations 500–1000 m above sea level, and very high altitude suggests elevations 1000+ m above sea level.

banana/sugarcane production. The prevalence of albuminuria was uniformly low across communities, and interestingly, 28% of men, most notably those men engaged in mining/subsistence farming, banana/sugarcane, and services, stated that they had been previously diagnosed with a urinary tract infection.

In the second study, Peraza *et al.* (12) sampled 664 residents between 20 and 60 years from five geographically varied communities in El Salvador who were involved in different industries: two sugarcane area (both 0–50 m above sea level), one sugarcane area (>500 m), one coffee production area (1650 m), and one services area (650 m) (12). In the two low-lying sugarcane communities, 19% of men had an eGFR less than 60 ml/min per 1.73 m² versus 2% in the high-altitude sugarcane community. Furthermore, age-adjusted duration of work in low-lying sugarcane communities was independently associated with a higher likelihood of reduced kidney function. Critically, both work tasks and agrichemical use in the sugarcane communities were similar regardless of altitude, with the major difference among the sugarcane communities being an average temperature that was 4°C lower in the community at high altitude. This work expanded on prior observations from a referral hospital in El Salvador. In this cohort comprised of 205 individuals initiating dialysis from November of 1999 to March of 2000, two-thirds lacked traditional kidney failure risk factors; these individuals were predominantly male farmers residing in coastal areas or close proximity to rivers, with previous exposure to insecticides and pesticides (9).

Potential Causes

There are multiple theories for the apparent excess of kidney disease in this region, and many of these theories are summarized in refs. 2 and 14. Hypotheses include heat stress, agrichemicals, heavy metals, aristolochic acid, medications and other toxins, including contaminants in locally distilled alcohols, infections such as leptospirosis, and genetic and developmental susceptibility factors. Very few kidney biopsies have been performed, particularly in earlier stages of disease, providing no histologic clues to etiology. The limited evidence available to date supporting and opposing several of these hypotheses is reviewed in Table 3. Critically, other potential causes certainly exist, and, as evidenced by the chain of events that led to the recognition of aristolochic acid as a nephrotoxin (16), it is quite possible that the cause of kidney disease may not be among those causes listed in Table 3 or that several of these possibilities may be acting together to result in CKD.

Toxins, including heavy metals, pesticides and herbicides, are potential causes of kidney disease in the region, reflecting prior and perhaps current environmental conditions and agricultural practices (17). Critically, if toxins that are filtered by the kidneys, such as heavy metals, contaminate drinking water, kidney toxicity could result from even apparently low concentrations of these toxins in the water supply, making the interpretation of environmental testing results more challenging. A possible discrepancy between environmental toxin concentration and individual person exposure could reflect the extremely high water

Table 3. Potential causes of endemic CKD in Central America

Possible Causes	Supporting Data	Opposing Data
Toxins Agrichemicals	Extensively used in the region High rates of CKD morbidity and mortality documented in areas with a high proportion of agricultural workers With high volume of water intake, low concentrations of toxins still may yield high kidney exposure High organophosphate exposure in El Salvador agricultural communities (35)	No single agrichemical linked to tubulointerstitial kidney disease without significant other organ involvement Similar agrichemicals used at higher altitudes, but CKD does not seem highly prevalent (12) High frequency of reduced eGFR found in occupations with no exposure to agrichemicals: miners, stevedores, and construction workers (3)
Heavy metals	Typically manifests with indolent tubulointerstitial nephritis Lack of sophisticated water delivery systems Active volcanic region Arsenic common in water and soil in region (36,37) Association between high urinary arsenic levels and low eGFR levels among 99 tested workers (3) With high volumes of water intake, low concentrations of toxins still may yield high kidney exposure	Limited evidence of high water levels of heavy metals, including cadmium, lead, arsenic, uranium, and 10 others in water samples tested one time in 2010 (3) No evidence of high urinary levels of cadmium, lead, or uranium or any association between these metals and reduced eGFR among 99 tested workers (3,11)
Aristolochic acid	Clinical course and manifestations consistent with Balkan endemic nephroathy Multiple species of Aristolochia present in Nicaragua and used for herbal remedies (38)	Limited overall opposing data, including male predilection, no reported increased risk of genitourinary tract malignancies, and use of herbal remedies containing Aristolochia, were documented only in Eastern Nicaragua, which is not known to be affected by the CKD epidemic (38)
Medications	Wide, poorly regulated availability of antibiotics, including aminoglycosides (29) Extensive use of nonsteroidal anti-inflammatory drugs (29)	Unusual cause of CKD in the absence of other factors, particularly in otherwise healthy individuals, but many, including nonsteroidal anti-inflammatory drug use, would predispose to kidney failure in the setting of other toxins
Infections Leptospirosis	Extremely common in Nicaragua (39) Associated with AKI High seroprevalence (39) Agricultural workers known to be a high-risk group (40)	Insufficient number of diagnosed cases to account for epidemic; prevalence of a chronic carrier state unknown Acute severe disease not subtle Uncertain link to CKD unless through AKI
Pyelonephritis	Pyuria and genitourinary symptoms common in local population, including men	Urine cultures in the setting of leukocyte esterase positivity or symptoms showed no growth in all 50 male workers tested, whereas 3 of 11 female workers had positive cultures (3)

Possible Causes	Supporting Data	Opposing Data
<p>Genetic or developmental</p> <p>Low birth weight (and therefore, low nephron mass) fairly common</p> <p>Genes associated with protection against tropical diseases seem to increase the risk of CKD among persons with African ancestry allelic variation, including Hispanic populations (41,42)</p> <p>Recognized CKD anecdotally more common in persons with greater indigenous ancestry</p>	<p>Low-altitude Western Nicaragua is hot and humid, and it is considered the hottest region in Nicaragua</p> <p>CKD more common among workers engaged in heavy manual labor, typically consisting of men</p> <p>CKD more common at lower altitudes</p>	<p>Anecdotally, on clinically performed ultrasonography, no evidence of systemic developmental or anatomic abnormalities</p> <p>Nothing is known about the genetic admixture of the local population or the prevalence of alleles that have been shown to be associated with an increased risk of CKD</p> <p>Greater indigenous ancestry associated with lower socioeconomic status, which is a risk factor for CKD in other populations</p>
<p>Volume depletion and heat-related</p>	<p>Heat-associated AKI is not common in high-income countries and when present, tends to manifest coincident with multiorgan organ injury</p> <p>Requires that AKI, either recognized or subclinical, be the cause of CKD</p> <p>No documentation of frequent episodes of clinically recognized AKI caused by heat-related causes</p>	<p>Heat-associated AKI is not common in high-income countries and when present, tends to manifest coincident with multiorgan organ injury</p> <p>Requires that AKI, either recognized or subclinical, be the cause of CKD</p> <p>No documentation of frequent episodes of clinically recognized AKI caused by heat-related causes</p>

References 3, 14, 19, and 29 (http://www.cao-ombudsman.org/cases/case_detail.aspx?id=82) have additional details regarding supporting and opposing data.

intake needed to replace volume losses, particularly among workers in very hot and humid conditions, which could result in significant kidney toxicity because of high net kidney exposure to potential environmental nephrotoxins as a function of total filtered load.

We find the hypothesis of heat stress, potentially superimposed on other factors, compelling and believe that it, in particular, requires additional investigation (18). Critical to this hypothesis is that CKD is occurring more often among individuals who have engaged in more strenuous physical activity in extreme environmental conditions. Sugarcane cutting is an exceptionally physically demanding task. On the night before harvesting, the cane field is burned, defoliating the field without damaging the cane stalk (Figure 1). The next morning, typically beginning before 6 a.m., cane cutters use machetes to harvest the cane as close to the base of the stalk as possible, with the average cutter harvesting between 5 and 7 tons of cane each day. The conditions can be oppressive, with a combination of very high temperatures, humidity, and solar radiation that sum to wet bulb globe temperatures above 30°C (with air temperatures often in the range of 38°C) by mid-morning in low-lying areas throughout the region (19,20). To place this information into context, the US Occupational Safety & Health Administration suggests that, for physically fit and temperature-acclimatized individuals wearing light summer clothing, each 15 minutes of heavy work in these conditions should be accompanied by 45 minutes rest to minimize the risk of exceeding a deep body temperature of 38°C (21).

Given the intensity of labor and the extreme conditions, the risk of heat stress and heat-related complications is high; accordingly, the risk of AKI would also be high. However, there are no published reports on the incidence of heat stroke in Nicaragua, although based on observations among workers and health care providers in the region, heat stroke does occur among workers, particularly earlier in the season when workers may not be acclimated. In observational studies in the general populations, including one study in Australia, heat waves are associated with increased likelihood of hospitalization for kidney-related disorders, including volume depletion and electrolyte abnormalities, with preexisting kidney disease an important risk modifier (22). Similar results have been seen during heat waves in California and Chicago, with AKI a more prominent cause of hospitalization during these episodes (23).

One major issue, particularly among workers engaged in strenuous physical activity, is volume depletion. Estimates from workers themselves in conjunction with observational reports suggest that anywhere from 5 to 15 L fluid intake is necessary to replace ongoing losses, with one small study interestingly showing that cane cutters who consumed more than 7 L water per day were more productive than those individuals consuming less water (24). Severe volume depletion can cause AKI in settings in which the degree of volume depletion exceeds the ability of counter-regulatory hormones to maintain end organ perfusion. The kidney is one of the most sensitive organs to acute changes in perfusion, and the risk of kidney ischemic injury may be particularly evident if the body’s ability to autoregulate glomerular filtration is impeded by agents like nonsteroidal anti-inflammatory drugs (NSAIDs) or if severe volume depletion occurs in the setting of other exogenous or endogenous nephrotoxins, such as

muscle breakdown products that can be present in exertional rhabdomyolysis (25,26). Serum creatinine typically returns to pre-morbid levels after acute ischemic injuries, and in the absence of comorbid conditions or active medical monitoring, kidney injury may remain subclinical or unrecognized.

Key to this hypothesis is that subclinical or undiagnosed episodes of AKI are occurring in this region; however, data to either strongly support or refute this hypothesis are lacking. Assuming that subclinical insults do occur and that these insults are repeated over time, what will be the chronic effect of these repeated insults on the kidney? Recently, a new paradigm has been gaining favor that AKI, even with apparent recovery in kidney function, may not be innocuous (27). In this paradigm, either repair attempts themselves or ongoing insults with subsequent repair attempts lead to a self-perpetuating cycle of inflammation and repair, resulting in kidney fibrosis and clinically recognizable CKD. Accordingly, we hypothesize that repeated ischemic insults to the kidney caused by severe volume depletion with or without hyperthermia and potentially in conjunction with other kidney insults result in progressive kidney fibrosis and ultimately, kidney failure.

Why Now and Why Here?

There are several possible reasons why this epidemic is either occurring now or, if the substrate has been present for some time, being recognized now. First, most cases of CKD in Central America are indolent, because the tempo of disease is fairly slow with few clinical manifestations until overt kidney failure is present. In 1970, the average life expectancy in Nicaragua was 53 years, rising to 73 years in 2009 (28). This dramatic improvement is multifactorial, reflecting improved sanitation and availability of treatments for infectious diseases. Because people live longer, deaths caused by kidney disease have increased opportunity to manifest, with the nonspecific symptoms of uremia not being attributed other conditions. Second, Nicaragua and other Central American nations have increasingly available health care. Although more elaborate care, including kidney replacement therapy, remains quite limited, increased awareness of chronic diseases and increased availability of simple serum creatinine tests mean that advanced CKD will less often go undiagnosed. Third, the world has become far less isolated, and reports of the unexpected are far more likely to be disseminated internationally. Based on discussions of CKD with Dr. Norman Jirón, one of the first practicing nephrologists in Nicaragua (D.R.B., personal communication), the prevalence of CKD in the northwest region of Nicaragua as far back as the 1970s seemed unusually high and manifested with many of the same features apparent in cases currently described, including young age of onset, male predominance, and employment in agrarian economic activity. Fourth, there may be new nephrotoxins present. Medications are widely available in Nicaragua without a prescription, and, for urinary syndromes, antibiotics are commonly prescribed, including intramuscular aminoglycosides (29). Additionally, NSAIDs are also widely used. One can envision the combination of aminoglycosides or NSAIDs with significant volume depletion enhancing the likelihood of developing AKI.

Implications and Future Directions

The epidemic of CKD in Nicaragua and elsewhere in Central America has important societal implications and potentially, worldwide relevance. Of note, there are several reports of multiple similar clusters of CKD worldwide; although many of these remain largely anecdotal, detailed descriptions exist for clusters in the Srikakulam District in Andhra Pradesh, India (30) and North Central Sri Lanka (31). In both of these settings, a tubulointerstitial pattern of kidney injury predominates, and, similar to northwestern Nicaragua and El Salvador, the climate is tropical, with many residents engaged in heavy, agricultural-based manual labor. In the coming years, as we confront global warming, population growth, and increased food and water scarcity (32), these extreme environments and working conditions may become more common, with CKD in Central America presaging a larger public health concern.

Ultimately, it is imperative that we gain a true understanding of the etiology of CKD in this region. In the coming years, we will continue to evaluate the epidemiology of CKD in Central America, assessing the presence of and predilection for CKD in various communities in this region, better defining the manifestations of CKD, and detailing the risk factors. In particular, we will evaluate the hypothesis that mild subclinical kidney injury can be induced by volume depletion in the extreme environmental conditions that are common in this region through novel use of AKI biomarkers in workers engaged in agricultural labor (33), with the overarching goal of preventing future cases of CKD.

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None.

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