


CONTINUING EDUCATION

Chronic Kidney Disease Among Workers

A Review of the Literature

Roxana Chicas, BSN, RN¹ , Jacqueline Mix, PhD¹, Valerie Mac, FNP-C, PhD¹, Joan Flocks, JD², Nathan Eric Dickman, PhD³, Vicki Hertzberg, PhD¹, and Linda McCauley, PhD, RN¹

Abstract: For the past two decades, agricultural workers in regions of Central America have reported an epidemic of chronic kidney disease of undetermined etiology (CKDu) that is not associated with established risk factors of chronic kidney disease. Several hypotheses have emerged, but the etiology of CKDu remains elusive and controversial. The aim of this literature review was to describe the potential risk factors of CKDu in Mesoamerica and implications for the U.S. agricultural worker population. PubMed and CINAHL databases were searched for articles published between 2000 and 2018 that examined CKDu in Mesoamerica; 29 original studies were included in this review. CKDu is a multifactorial disease that is often asymptomatic with hallmark characteristics of elevated serum creatinine and blood urea nitrogen (BUN), low glomerular filtration rate, electrolyte abnormalities, and non-nephrotic proteinuria. Reducing the global prevalence of CKDu will require more robust studies on causal mechanisms and on interventions that can reduce morbidity and mortality in vulnerable populations.

Keywords: agricultural workers, occupational hazards, chronic kidney disease, CKDu, Mesoamerican nephropathy, agricultural communities

Introduction

Chronic kidney disease of unknown etiology (CKDu) presents as chronic kidney disease (CKD) without traditional risk factors such as diabetes, hypertension, cardiovascular disease, or older age at onset (Crowe et al., 2013). During the past 40 years, a global epidemic of CKDu has emerged among young male agricultural workers in regions of Mesoamerica (central Mexico, Belize, Guatemala, El Salvador, Honduras, Nicaragua, and northern Costa Rica), South Asia, and Eastern Europe (F. Gifford et al., 2016; Wesseling et al., 2015). With

more than 20,000 documented deaths, the Pan American Health Organization (PAHO) called attention to this growing epidemic in 2013 (Pan American Health Organization, 2013).

There is a compelling, urgent need to investigate the factors associated with the development of CKDu, including biomarkers that might indicate early pathology, such as renal dysfunction. CKDu has not been reported in the United States (U.S.), but renal dysfunction in U.S. agricultural workers who have immigrated from Mesoamerica has been documented in studies of physiological responses to environmental heat (Horton, 2016; Mix et al., 2018; Moyce, Joseph, Tancredi, Mitchell, & Schenker, 2016). Renal dysfunction among agricultural workers in California's Central Valley and in Florida suggests the potential of an emerging public health concern in the U.S. Agricultural workers in the U.S. and Mesoamerica have similar environmental and occupational exposures that are potentiated by social and economic factors, such as extreme poverty, which may obligate workers to labor in extreme and harsh conditions (Crowe et al., 2013; Horton, 2016; Jackson & Rosenberg, 2010; Wesseling, Aragon, Gonzalez, Weiss, Glaser, Bobadilla, et al., 2016). Workers are also vulnerable due to lack of regulations to protect workers from occupational heat exposure. In Costa Rica and the U.S. states (California and Washington) where regulations do exist, workers exhibit kidney dysfunction and heat-related illness symptoms (Crowe, Nilsson, Kjellstrom, & Wesseling, 2015; Moyce et al., 2016) which may suggest a lack of enforcement. This article reviews the CKDu epidemic in Mesoamerica, clinical characteristics of it, proposed hypotheses for the CKDu epidemic, and provides implications for occupational health nursing research and practice.

Method

The databases PubMed and CINAHL were searched for published studies from 2000 to 2018 conducted in Mesoamerica

examining CKDu. Primary search terms were “chronic kidney disease of unknown etiology,” “Mesoamerican nephropathy,” “agricultural nephropathy,” “CKDu,” and “Mesoamerica.” Articles were considered relevant and included in the review if they (a) evaluated CKDu in agricultural workers, (b) were conducted in Mesoamerica, and (c) were published in English.

Results

Twenty-nine articles were found that met the inclusion criteria. The types of studies were classified as descriptive clinical features ($n = 4$), data-based epidemiological studies ($n = 4$), a case-control study ($n = 1$), longitudinal studies ($n = 5$), cross-sectional studies ($n = 12$), a qualitative study ($n = 1$), and intervention studies ($n = 2$). The following sections describe the main topics in the papers located in this search.

Clinical Features of CKDu

A cross-sectional study in El Salvador of 205 patients was the first published study to observe 67% of the patients with end-stage renal disease (ESRD) who did not have the traditional known risk factors for developing CKD and ESRD and were predominately young male agricultural workers (Trabanino, Aguilar, Silva, Mercado, & Merino, 2002). Since then, multiple studies have been conducted, but there is still an uncertainty on the natural progression of CKDu. The majority of the studies examined workers or communities at risk and very few on the pathophysiology of CKDu. Currently, a consistent case definition for CKDu does not exist, but the review of the literature revealed that the following factors are being used to indicate renal dysfunction in study populations without traditional risk factors of CKD: serum creatinine (SCr) >1.2 mg/dL or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (Peraza et al., 2012; Raines et al., 2014; Sanoff et al., 2010; Torres et al., 2010) or an eGFR <60 mL/min/1.73 m² after 3 months (Orantes et al., 2011; Orantes et al., 2014). Cross-shift and across harvest studies used the Kidney Disease Improving Global Outcomes (KDIGO) criteria for acute kidney injury (AKI), a risk factor for CKD: elevated SCr (development of AKI increased ≥ 0.3 mg/dL or ≥ 1.5 -fold from baseline); eGFR below 60 mL/min/1.73 m² at more than one time point showing chronicity (Garcia-Trabanino et al., 2015; F. J. Gifford, Gifford, Eddleston, & Dhaun, 2017; Khwaja, 2012). In addition to trace proteinuria, hypokalemia, hyponatremia, and hyperuricemia, no established risk factors of CKD presented prior to the onset of disease (Kupferman et al., 2016; Laws et al., 2016). Clinical diagnosis may include ultrasounds showing small echogenic kidneys (Herrera et al., 2014) and kidney biopsy samples indicate glomerular lesions and tubulointerstitial damage, suggesting chronic ischemia and mild vascular changes not consistent with other common renal diseases (Lopez-Marín et al., 2014; Wijkstrom et al., 2013). In one study, an increase in the renal biomarkers of tubular damage in AKI was also present in those with CKDu (Laws et al., 2016). Biomarkers observed in this study included albumin-creatinine ratio (ACR), neutrophil

gelatinase-associated lipocalin (NGAL), *N*-acetyl-D-glucosaminidase (NAG), and interleukin-18 (IL-18). In two other studies, symptoms reported included headaches, nausea, fever, muscle cramps, dizziness, dysuria, swelling of hands and feet, and dyspnea (Crowe et al., 2015; Herrera et al., 2014).

Without a consistent case definition of CKDu, it was not possible to compare the incidence across different populations, and the ability to examine etiological factors was limited. Due to this limitation, recently, the Disadvantaged Populations eGFR Epidemiology (DEGREE) protocol initiative has called for standardization of SCr measurements, storage of cystatin C, body composition measurements, and self-reported meat consumption which fosters comparison of findings across studies conducted in different countries (Caplin et al., 2017).

Etiologic Hypotheses for CKDu

Although there is not a widely accepted case definition for CKDu, there are many etiologic hypotheses including heat stress and volume depletion, agrochemical exposure, nephrotoxicity, and infection, which may interact with host factors including genetics and socioeconomic status.

Heat Stress, Dehydration, and Volume Depletion

A mechanism for CKDu proposed by several researchers is that occupational heat stress leads to chronic dehydration, which disrupts kidney function (Carl-Gustaf, Wernerson, & Wijkstrom, 2015; Correa-Rotter, Wesseling, & Johnson, 2014). Strenuous occupational work in environments with high ambient temperatures has been commonly reported, where dehydration was common (Garcia-Trabanino et al., 2015; Wesseling, Aragon, Gonzalez, Weiss, Glaser, Bobadilla, et al., 2016; Wesseling, Aragon, Gonzalez, Weiss, Glaser, Rivard, et al., 2016). Studies observed that workers lost up to 2.5 kg during single work shifts with urine-specific gravity (USG) measurements at the end of work shifts that indicated dehydration (Garcia-Trabanino et al., 2015). Decreased kidney function was more often observed in regions with high ambient temperatures, such as coastal communities, than in high-altitude communities (Laux, Barnoya, Guerrero, & Rothstein, 2015; Peraza et al., 2012; Torres et al., 2010; Wesseling et al., 2015). Studies have observed, across a harvest season, a reduction in eGFR and SCr at the beginning and end of a harvest season, and an increase in acute renal injury biomarkers at the end of the season (Laws et al., 2015, 2016; Wesseling, Aragon, Gonzalez, Weiss, Glaser, Bobadilla, et al., 2016). These findings suggest that occupational heat stress and recurrent dehydration may be associated with the development of CKDu. There was consensus during the first and second International Research Workshops on CKDu that repeated episodes of dehydration during heavy work in hot climates, with loss of electrolytes accompanied by AKI, may be a significant contributing factor to the CKDu epidemic (Wesseling et al., 2014). However, it is noteworthy that chronic dehydration has not been recognized as a cause of CKD, but rather a known contributing factor to

AKI. Consensus in the medical literature indicates that hospitalized patients who suffer from AKI due to dehydration fully recover renal function after an acute event (National Health Service, 2016). There is no strong evidence to date that repeated episodes of AKI are part of the natural history of CKDu and recovery from AKI episodes eventually diminishes and leads to permanent renal disease. Only one paper focused on patients diagnosed with CKDu and potential risk factors (VanDervort, Lopez, Orantes, & Rodriguez, 2014). In reviewing medical records and place of residence, this ecological study reported no association between patients hospitalized with CKDu and ESRD and ambient temperatures in areas of residence.

A study among 117 agricultural workers in Nicaragua hypothesized that consuming high-fructose drinks and chewing sugarcane during strenuous work activity were etiological risk factors for the development of CKDu (Raines et al., 2014). The researchers suggested that excessive intake of fructose may exacerbate kidney injury via the fructokinase pathway. However, there have been no human studies documenting a relationship between ingestion of high-fructose beverages and the development of CKDu. A rodent study has shown that repeated dehydration leads to fructokinase activity, which results in tubular injury from the generation of endogenous fructose via the polyol pathway (Roncal Jimenez et al., 2014). This suggests that excessive intake of fructose beverages may exacerbate kidney injury; however, further research is warranted to translate these findings to human populations.

Agrochemical Exposure

Agrochemicals such as pesticides and fertilizers have been postulated as risk factors for CKDu (Jayasumana et al., 2017; O'Donnell et al., 2011; Orantes et al., 2014; Raines et al., 2014). Agricultural workers are exposed to agrochemicals through ingestion, inhalation, and dermal contact of pesticides and fertilizers that are applied at the worksite. However, in a longitudinal cohort study in Nicaragua, agrochemical applicators did not have a significant increase in renal injury biomarkers (Laws et al., 2016). A cross-sectional study in Nicaragua among small-scale farmers, construction workers, and sugarcane cutters did not observe an association between pesticides and biomarkers of kidney function (Wesseling, Aragon, Gonzalez, Weiss, Glaser, Rivard, et al., 2016). An ecological study of patients in El Salvador with CKDu conducted by VanDervort et al. (2014) postulated that the disease might arise from proximity to agricultural fields to which agrochemicals had been applied. However, a systematic review found no significant association between pesticides and CKDu (Gonzalez-Quiroz, Pearce, Caplin, & Nitsch, 2018). To date, there have been no studies in Mesoamerica examining biomarkers of agrochemical exposure; only self-reports of work practices and history have been obtained through questionnaires.

While pesticide exposure has been frequently reported in agricultural workers, kidney damage has also been reported in

case studies of females and adolescents who had no prior agricultural work history (Ramirez-Rubio et al., 2016). If agrochemicals contribute to CKDu, nonworker exposure to agrochemicals through ingestion, inhalation, or dermal contact within the same living environment as workers may also contribute to kidney damage.

Nephrotoxin Exposure

Exposure to heavy metals and certain medications can be toxic to the kidneys. A study in Western Nicaragua found lead, cadmium, arsenic, and uranium in soil and water, but at nontoxic levels and not specifically in the areas where CKDu is prevalent (McClellan et al., 2012). Other studies from Nicaragua reported that a locally produced form of alcohol was prepared and stored in industrial metal containers and that this may have exposed agricultural workers who drank the alcohol to lead, cadmium, or other heavy metals that are nephrotoxic; however, the study did not identify specific nephrotoxic agents that were present (Lebov et al., 2015; Sanoff et al., 2010).

Chronic consumption of nonsteroidal anti-inflammatory drugs (NSAIDs) and aminoglycoside antibiotics has also been shown to be a risk factor of CKDu (Wesseling et al., 2014). Agricultural workers are engaged in strenuous work that can cause workplace injuries, musculoskeletal disorders, and resulting pain. These workers may alleviate their symptoms with NSAIDs (Herrera et al., 2014; Orantes et al., 2011). Another common symptom of CKDu is dysuria, and workers may self-prescribe aminoglycoside antibiotics which are poorly regulated in Mesoamerica (Ramirez-Rubio et al., 2013).

Leptospira Infection

Leptospirosis is a widespread zoonotic disease that can be transmitted to humans through soil or water contaminated by infected animal urine. Agricultural workers may be exposed to *Leptospira* bacteria in soil and water during cultivation and harvesting tasks. Surveillance data from a Nicaraguan hospital reported an outbreak of leptospirosis in 1998, a peak in 2001, and an endemic cycle consistent with El Niño–Southern Oscillation weather patterns (Murray et al., 2015). In a longitudinal study in Nicaragua, seropositive sugarcane workers had higher NGAL concentrations (relative mean = 1.28; 95% confidence interval [CI] = [0.94, 1.75]) (Riefkohl et al., 2017). Leptospirosis is an asymptomatic infection, and those with severe *Leptospira* infection sometimes present with AKI. Although it has not been established that acute *Leptospira* infection leads to CKDu, it may be a factor that increases susceptibility to CKDu (Yang, 2018).

Genetic Factors

Advances in genetic research have shown that the prevalence and risk of developing traditional CKD can vary according to ethnicity, so genetics may also play a role in the development of CKDu. A study conducted among 200 nonworking Nicaragua adolescents (ages 12–18 years) from four

different school locations (Ramirez-Rubio et al., 2016) assessed biomarkers of kidney injury including the ACR, NGAL, NAG, and IL-18. Elevated renal biomarker levels were observed in adolescents in regions with higher comparative CKDu mortality rates (Ramirez-Rubio et al., 2016). Familial clustering suggested possible genetic susceptibility and/or hazardous environmental exposure; however, the study did not assess these factors. Furthermore, renal biomarkers assessed do not have established normal values for adolescents, making comparison with adult populations difficult.

Socioeconomic Risk Factors

Risk factors for CKDu are potentiated by social and economic factors such as extreme poverty, which obligates workers to work in extreme and harsh conditions (Bodin et al., 2016; Crowe et al., 2013; Wesseling et al., 2014; Wesseling, Aragon, Gonzalez, Weiss, Glaser, Bobadilla, et al., 2016). Studies in Nicaragua found agricultural fieldworkers to be at greater risk of decline in kidney function as compared with nonfieldworkers (Laws et al., 2015; Torres et al., 2010; Wesseling, Aragon, Gonzalez, Weiss, Glaser, Rivard, et al., 2016). Factors such as poor hydration, lack of rest breaks, lack of heat-related illness prevention training, use of clothing or equipment that increases body heat or decreases the efficiency of sweat evaporation, low wages, and lack of sufficient workplace regulation can further complicate heat stress.

Intervention Studies

To date, the only intervention study that has been conducted in the Mesoamerican region has been an adapted protocol from the Occupational Safety and Health Administration's (OSHA) "Water, Rest, Shade." (WRS) program in El Salvador (Bodin et al., 2016; Wegman et al., 2018). Sugarcane workers were given Camelback™ water backpacks, mobile shade structures, scheduled rest periods, and ergonomically improved machetes. The results were an increase in quantity of sugarcane harvested, a reduction in symptoms associated with heat stress and dehydration, and an increase in water consumption (Bodin et al., 2016). Although the decrease in eGFR was less for the intervention group ($-3.4 \text{ mL/min/1.73 m}^2$) compared with the control group ($-5.3 \text{ mL/min/1.73 m}^2$), additional research is necessary to assess whether the intervention can reduce the risk of developing CKDu (Wegman et al., 2018). Furthermore, it is important to note that this intervention study was developed under the hypothesis that heat stress was an etiological factor of CKDu.

U.S. Studies

Despite no clear pattern of risk factors associated with CKDu, recent reports have suggested that workers from Mesoamerica who are employed in the U.S. also exhibit signs of kidney injury. In Central Valley, California, there were anecdotal reports of AKI and CKD among migrant agricultural workers (Horton, 2016). A study conducted in Central Valley, California,

with 295 agricultural workers found that 12% had pre- to postwork shift increases in SCr of at least 0.3 mg/dL or 1.5 times the preshift value, AKI according to the KDIGO criteria (Moyce et al., 2016).

Findings from a Florida study showed that agricultural workers lived in a state of chronic dehydration and experience elevated core body temperature while working (Mac et al., 2017). Of the 192 agricultural workers, 53% started their workday in a dehydrated state ($\text{USG} \geq 1.020$), and 78% were dehydrated by the end of the workday (Mix et al., 2018). On at least one of three workdays, 33% of workers experienced pre- to postwork shift SCr increases of at least 0.3 mg/dL or 1.5 times the preshift value, AKI using the KDIGO criteria, and for each 5°F increase in heat index, the odds of AKI increased 37% (Mix et al., 2018).

Discussion

This literature review describes published evidence regarding the clinical manifestation and possible etiological factors associated with CKDu in Mesoamerican populations. These results demonstrate that there is no consistent definition or gold standard for CKDu; nevertheless, the epidemiological evidence of an increase in mortality from a type of kidney disease that does not fit the usual pattern of CKD is compelling. Possible etiological factors include heat stress, pesticide exposure, genetic susceptibility, heavy metals, and medications.

Further research is needed to provide valid and reliable assessment of biomarkers of agrochemicals, hydration, and renal injury among diverse communities in occupational settings. Although existing CKDu studies provide useful data on risk factors, further longitudinal epidemiological studies are needed to address reverse causality. In addition, a consistent case definition of CKDu and methodology are needed to conduct better research studies where measures are comparable across different populations. Joint studies of the prevalence and incidence of AKI and CKDu among agricultural workers in the U.S. and the Mesoamerican region are also needed to monitor the disease at a global level.

Implications for Occupational Health Nursing

Reports of AKI and CKD in the U.S.-based agricultural worker population and studies showing chronic dehydration in agricultural workers call for careful vigilance. Occupational health nurses can play important roles in recognizing kidney disease among agricultural workers, advocating for heat stress prevention strategies and conducting research on etiological factors and interventions to decrease heat stress in workers.

Occupational and community health nurses should assess work histories to identify patient occupation, provide guidance in the management of musculoskeletal pain to prevent overuse of NSAIDs, educate patients on the potential risks of self-treatment with antibiotics for urinary symptoms, and encourage patients to seek professional care for urinary symptoms to

Table 1. Studies Pertaining to Acute Kidney Injury and Chronic Kidney Disease of Unknown Etiology (CKDu) Among Mesoamerican Workers

Author (year)	Study design/population	Proposed risk factor(s)	Outcome	Findings	Limitations
Heat stress/dehydration/volume depletion					
García-Trabanino et al. (2015)	Cross-sectional/agricultural workers in El Salvador	Occupation Geography Temperature	Renal biomarkers Temperature	WBGT and postshift increase in SCr ($p = .001$) and reduced eGFR ($p = .001$)	Causality not addressed One-time point measurement
Wesseling, Aragon, Gonzalez, Weiss, Glaser, Rivard, et al. (2016)	Cross-sectional/sugarcane cutters, construction workers, and farmers in Nicaragua	Occupation	Renal biomarkers	Reduced eGFR occurred in sugarcane cutters 16%, construction workers 9%, and farmers 2%, respectively ($p = .003$)	Causality not addressed One-time point measurement
Wesseling, Aragon, Gonzalez, Weiss, Glaser, Bobadilla, et al. (2016)	Longitudinal/sugarcane cutters in Nicaragua	Occupation	Renal biomarkers	At end of harvest eGFR decreased (9%, $p = .02$), and NGAL increased four times ($p = .001$)	Sample size small and attrition high
Wesseling et al. (2015)	Ecological/mortality records in Costa Rica	Geography Climate Crops	Mortality data Temperature Crops	Sugarcane production areas had higher mortality rate among men (38.5 per 100,000)	Lack of available data on relevant confounding factors
Laux, Barnoya, Guerrero, and Rothstein (2015)	Ecological/dialysis enrollment records in Guatemala	Occupation Geography	Dialysis enrollment	Dialysis enrollment is higher in males in the Southwest (higher temperature and sugarcane-growing region; $p < .01$)	Lack of available data on relevant confounding factors
Peraza et al. (2012)	Cross-sectional/agricultural and nonagricultural workers in El Salvador	Occupation Geography	Renal biomarkers	Increased SCr in agricultural male workers in coastal area (OR = 3.1, 95% CI = [2.0, 5.0])	Causality not addressed One-time point measurement
Laws et al. (2015)	Longitudinal/sugarcane and factory workers in Nicaragua	Occupation Temperature	Renal biomarkers	Field workers (heat exposed) decreased eGFR (95% CI = [-12.3, -3.2]) at end of harvest	Did not consider relevant confounders
Laws et al. (2016)	Longitudinal cohort/sugarcane and factory workers in Nicaragua	Occupation Geography	Renal biomarkers	Sugarcane workers had a change NGAL during the harvest (RM = 1.49, 95% CI = [1.07, 2.09]), IL-18 (RM = 1.61, 95% CI = [1.12, 2.31]), and NAG (RM = 2.92, 95% CI = [2.08, 4.10])	Renal biomarkers assessed do not have established normal values for field-based studies in this population
VanDervort, Lopez, Orantes, and Rodriguez (2014)	Ecological/patient medical records in El Salvador	Occupation Climate	Temperature Crops	CKDu patients and percent area of sugarcane, corn, and cotton harvest ($p < .001$) No association found with heat	Did not consider relevant confounders

(continued)

Table 1. (continued)

Author (year)	Study design/population	Proposed risk factor(s)	Outcome	Findings	Limitations
Agrochemical exposure					
Raines et al. (2014)	Cross-sectional/agricultural workers in Nicaragua	Occupation Geography Pesticides	Renal biomarkers	Reduced eGFR and pesticide exposure (OR: 3.31, 95% CI = [1.32, 8.31])	Self-reported questionnaire Causality not addressed
Orantes et al. (2014)	Cross-sectional/residents of three municipalities in El Salvador	Occupation Agrochemicals Health history	Renal biomarkers	Reduced eGFR with exposure to methyl parathion (POR = 2.6, 95% CI = [1.239, 5.448])	Self-reported questionnaire Causality not addressed
O'Donnell et al. (2011)	Case-control/residents of Quezalguaque, Nicaragua	Occupation Agrochemicals	Renal biomarkers	Pesticide exposure (OR = 1.85, 95% CI = [0.84, 4.07])	Small sample size Self-reported questionnaire
Nephrotoxins exposure					
McClean et al. (2012)	Longitudinal/sugarcane workers, miners, and factory workers in Nicaragua	Occupation Heavy metals	Biomarkers of lead, cadmium, arsenic, and uranium Renal biomarkers	Increased Scr ($p = .04$) and significantly lower eGFR ($p = .01$) in workers with highest arsenic exposure	Attrition high
Lebov et al. (2015)	Cross-sectional/residents of León, Nicaragua	Occupation Homemade alcohol consumption	Renal biomarkers	Decreased eGFR and drinking homemade alcohol (POR = 1.95, 95% CI = [1.13, 3.38])	Self-reported questionnaire Causality not addressed
Sanoff et al. (2010)	Cross-sectional/residents of nine municipalities in Nicaragua	Occupation Homemade alcohol consumption	Renal biomarkers	Decreased eGFR with consumption of homemade alcohol (OR = 2.10, 95% CI = [1.305, 3.386])	Self-reported questionnaire Causality not addressed
Herrera et al. (2014)	Cross-sectional/Patients diagnosed with CKDu in El Salvador	Occupation Alcohol Medications	Medication and Occupational history	41% reported NSAID use	Small sample size Self-reported questionnaire Causality not addressed
Orantes et al. (2011)	Cross-sectional/residents of three municipalities in El Salvador	Occupation Medications	eGFR	75% reported NSAID use	Self-reported questionnaire Causality not addressed
Ramirez-Rubio et al. (2013)	Qualitative/physicians and pharmacist in Nicaragua	Dysuria-related symptoms	Determine practices of UTI diagnosis and medication	Antibiotics sold without a prescription or formal diagnosis. Gentamicin prescribed when other antibiotics are unavailable	Small sample size Unable to test statistical significance

(continued)

Table 1. (continued)

Author (year)	Study design/population	Proposed risk factor(s)	Outcome	Findings	Limitations
<i>Leptospira</i> infection					
Murray et al. (2015)	Ecological/patient medical records and weather pattern data in Nicaragua	El Niño-southern oscillation (ENSO) weather patterns	AKI	Acute kidney injury outbreak curve correlate with the El Niño-southern oscillation (ENSO) weather patterns. Outbreaks of leptospirosis concentrated along the Pacific coastal region	Did not test statistical significance
Riefkohl et al. (2017)	Longitudinal cohort/sugarcane and factory workers in Nicaragua	Occupation	Anti-leptospiral antibodies, renal biomarkers	<i>Leptospira</i> seropositive in sugarcane workers had higher NGAL (RM = 1.28; 95% CI = [0.94, 1.75])	Attrition high
Genetic factors					
Ramirez-Rubio et al. (2016)	Cross-sectional/adolescents in Nicaragua	Environment family health history	Renal biomarkers	Higher concentrations of MAG in adolescents in region of high CKD mortality (boys RM = 2.40, 95% CI = [1.18, 4.86] for boys; girls RM = 2.01, 95% CI = [1.36, 2.96])	Renal biomarkers assessed do not have established normal values for adolescents
Socioeconomic factors					
Torres et al. (2010)	Cross-sectional/agriculture, fishing, mining, construction, service workers in Nicaragua	Occupation Geography Hypertension	Renal biomarkers	Increase SCr in banana/sugarcane workers (OR = 3.39, 95% CI = [1.67, 6.91])	Causality is not addressed
Crowe et al. (2013)	Cross-sectional/nonparticipatory observation of sugarcane workers in Costa Rica	Occupation Climate Metabolic demand	WBGT Metabolic load	Metabolic load of 261 W/m ² (6.8 kcal/min), and by 7:30 a.m. the WBGT reached 26°	Did not consider relevant confounders
Intervention studies					
Bodin et al. (2016)	Longitudinal intervention/sugarcane workers in El Salvador	Occupation Climate Heat stress	WBGT symptoms of heat stress and water consumption	Increased water consumption by an average of 1.2 L (95% CI = [0.8, 1.6]) and decrease in reported symptoms of heat stress	Small sample size
Wegman et al. (2018)	Longitudinal intervention/sugarcane workers in coastland and inland in El Salvador	Occupation Climate Heat Stress	Renal biomarkers	Inland postintervention group eGFR -0.15 percentage points/month (95% CI = [-1.05, 0.75])	Small sample size Postintervention coastland group data unavailable

Note: CKDu = chronic kidney disease of unknown etiology; WBGT = Wet Bulb Globe Temperature; SCr = serum creatinine; eGFR = estimated glomerular filtration rate; NGAL = neutrophil gelatinase-associated lipocalin; OR = odds ratio; CI = confidence interval; RM = relative mean; IL-18 = interleukin-18; MAG = *N*-acetyl- α -glucosaminidase; POR = prevalence odds ratio; NSAID = nonsteroidal anti-inflammatory drugs; ENSO = El Niño-southern oscillation; AKI = acute kidney injury; UTI = urinary tract infection.

decrease the risk of AKI. Examination should include assessing SCr and eGFR for patients identified as high risk based on their medical and occupational history and presenting symptoms. Strategies to combat an epidemic of CKDu include instructions to drink 8 oz of water every 15 to 20 minutes for work periods of moderate exertion, with the incorporation of a sports drink containing electrolytes and low sugar for prolonged work periods with excessive sweating (Jacklitsch, Musolin, Coca, Kim, & Turner, 2016) (Table 1).

Conclusion

Evidence suggests that CKDu is a multifactorial disease. Preventive approaches are key to reducing the morbidity and mortality associated with CKDu and to relieving the global burden on disadvantaged populations, such as agricultural workers. Many of the proposed hypotheses about the cause of CKDu relate to behaviors that can be changed via occupational health and safety training and public health policies that protect agricultural workers. More research is needed to understand the complexity in the interactions between global exposures and local factors and behavior practices. Reducing the global prevalence of CKDu will require more robust studies on causal mechanisms and on interventions that can reduce morbidity and mortality in vulnerable populations.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Roxana Chicas  <https://orcid.org/0000-0002-6715-1618>

References

- Bodin, T., Garcia-Trabanino, R., Weiss, I., Jarquin, E., Glaser, J., Jakobsson, K., . . . Wegman, D. H. (2016). Intervention to reduce heat stress and improve efficiency among sugarcane workers in El Salvador: Phase 1. *Occupational and Environmental Medicine*, *73*, 409-416. doi:10.1136/oemed-2016-103555
- Caplin, B., Jakobsson, K., Glaser, J., Nitsch, D., Jha, V., Singh, A., . . . Pearce, N. (2017). International collaboration for the epidemiology of eGFR in low and Middle Income populations—Rationale and core protocol for the Disadvantaged Populations eGFR Epidemiology Study (DEGREE). *BMC Nephrology*, *18*, Article 1. doi:10.1186/s12882-016-0417-1
- Carl-Gustaf, E., Wernerson, A., & Wijkstrom, J. (2015). Mesoamerican Nephropathy (MeN): A “new” chronic kidney disease related to occupational heat exposure with repeated deprivation of salts and water. *International Journal of Nephrology and Kidney Failure*, *1*(2). doi:10.16966/2380-5498.109
- Correa-Rotter, R., Wesseling, C., & Johnson, R. J. (2014). CKD of unknown origin in Central America: The case for a Mesoamerican nephropathy. *American Journal of Kidney Diseases*, *63*, 506-520. doi:10.1053/j.ajkd.2013.10.062
- Crowe, J., Nilsson, M., Kjellstrom, T., & Wesseling, C. (2015). Heat-related symptoms in sugarcane harvesters. *American Journal of Industrial Medicine*, *58*, 541-548. doi:10.1002/ajim.22450
- Crowe, J., Wesseling, C., Solano, B. R., Umana, M. P., Ramirez, A. R., Kjellstrom, T., . . . Nilsson, M. (2013). Heat exposure in sugarcane harvesters in Costa Rica. *American Journal of Industrial Medicine*, *56*, 1157-1164. doi:10.1002/ajim.22204
- Garcia-Trabanino, R., Jarquin, E., Wesseling, C., Johnson, R. J., Gonzalez-Quiroz, M., Weiss, I., . . . Barregard, L. (2015). Heat stress, dehydration, and kidney function in sugarcane cutters in El Salvador—A cross-shift study of workers at risk of Mesoamerican nephropathy. *Environmental Research*, *142*, 746-755. doi:10.1016/j.envres.2015.07.007
- Gifford, F., Kimmitt, R., Herath, C., Webb, D. J., Melville, V., Siribaddana, S., . . . Dhaun, N. (2016). Arterial stiffness & Sri Lankan chronic kidney disease of unknown origin. *Scientific Reports*, *6*, Article 32599. doi:10.1038/srep32599
- Gifford, F. J., Gifford, R. M., Eddleston, M., & Dhaun, N. (2017). Endemic nephropathy around the world. *Kidney International Reports*, *2*, 282-292. doi:10.1016/j.ekir.2016.11.003
- Gonzalez-Quiroz, M., Pearce, N., Caplin, B., & Nitsch, D. (2018). What do epidemiological studies tell us about chronic kidney disease of undetermined cause in Meso-America? A systematic review and meta-analysis. *Clinical Kidney Journal*, *11*, 496-506. doi:10.1093/ckj/sfx136
- Herrera, R., Orantes, C. M., Almaguer, M., Alfonso, P., Bayarre, H. D., Leiva, I. M., . . . Aparicio, C. E. (2014). Clinical characteristics of chronic kidney disease of nontraditional causes in Salvadoran farming communities. *MEDICC Review*, *16*(2), 39-48.
- Horton, S. B. (2016). *They leave their kidneys in the fields: Illness, injury, and illegality among U.S. farmworkers* (Vol. 40). Berkeley: University of California Press.
- Jacklitsch, B. W. W., Musolin, K., Coca, A., Kim, J.-H., & Turner, N. (2016). *NIOSH criteria for a recommended standard: Occupational exposure to heat and hot environments* (NIOSH Publication No. 2016-106). Cincinnati, OH: National Institute for Occupational Safety and Health. Retrieved from <https://www.cdc.gov/niosh/docs/2016-106/pdfs/2016-106.pdf>
- Jackson, L. L., & Rosenberg, H. R. (2010). Preventing heat-related illness among agricultural workers. *Journal of Agromedicine*, *15*, 200-215.
- Jayasumana, C., Orantes, C., Herrera, R., Almaguer, M., Lopez, L., Silva, L. C., . . . De Broe, M. E. (2017). Chronic interstitial nephritis in agricultural communities: A worldwide epidemic with social, occupational and environmental determinants. *Nephrology Dialysis Transplantation*, *32*, 234-241. doi:10.1093/ndt/gfw346
- Khwaja, A. (2012). KDIGO clinical practice guidelines for acute kidney injury. *Nephron Clinical Practice*, *120*(4), c179-c184.
- Kupferman, J., Amador, J. J., Lynch, K. E., Laws, R. L., Lopez-Pilarte, D., Ramirez-Rubio, O., . . . Friedman, D. J. (2016). Characterization of Mesoamerican nephropathy in a kidney failure hotspot in Nicaragua. *American Journal of Kidney Diseases*, *68*, 716-725. doi:10.1053/j.ajkd.2016.06.012
- Laux, T. S., Barnoya, J., Guerrero, D. R., & Rothstein, M. (2015). Dialysis enrollment patterns in Guatemala: Evidence of the chronic kidney disease of non-traditional causes epidemic in Mesoamerica. *BMC Nephrology*, *16*, Article 54. doi:10.1186/s12882-015-0049-x
- Laws, R. L., Brooks, D. R., Amador, J. J., Weiner, D. E., Kaufman, J. S., Ramirez-Rubio, O., . . . McClean, M. D. (2015). Changes in kidney

- function among Nicaraguan sugarcane workers. *International Journal of Occupational and Environmental Health*, 21, 241-250. doi:10.1179/2049396714y.0000000102
- Laws, R. L., Brooks, D. R., Amador, J. J., Weiner, D. E., Kaufman, J. S., Ramirez-Rubio, O., . . . McClean, M. D. (2016). Biomarkers of kidney injury among Nicaraguan sugarcane workers. *American Journal of Kidney Diseases*, 67, 209-217. doi:10.1053/j.ajkd.2015.08.022
- Lebov, J. F., Valladares, E., Pena, R., Pena, E. M., Sanoff, S. L., Cisneros, E. C., . . . Hogan, S. L. (2015). A population-based study of prevalence and risk factors of chronic kidney disease in Leon, Nicaragua. *Canadian Journal of Kidney Health and Disease*, 2, Article 6. doi:10.1186/s40697-015-0041-1
- Lopez-Marin, L., Chavez, Y., Garcia, X. A., Flores, W. M., Garcia, Y. M., Herrera, R., . . . Serpas, L. (2014). Histopathology of chronic kidney disease of unknown etiology in Salvadoran agricultural communities. *MEDICC Review*, 16(2), 49-54.
- Mac, V. V., Tovar-Aguilar, J. A., Flocks, J., Economos, E., Hertzberg, V. S., & McCauley, L. A. (2017). Heat exposure in central Florida fernery workers: Results of a feasibility study. *Journal of Agromedicine*, 22, 89-99. doi:10.1080/1059924x.2017.1282906
- McClean, M., Amador, J. J., Laws, R., Kaufman, J. S., Weiner, D. E., Rodríguez, J. M. S., . . . Brooks, D. (2012). *Biological sampling report: Investigating biomarkers of kidney injury and chronic kidney disease among workers in Western Nicaragua*. Boston, MA: Boston University School of Public Health.
- Mix, J., Elon, L., Mac, V., Flocks, J., Economos, E., Tovar-Aguilar, A. J., . . . McCauley, L. A. (2018). Hydration status, kidney function, and kidney injury in Florida agricultural workers. *Journal of Occupational and Environmental Medicine*, 60(5): e253-e260. doi:10.1097/jom.0000000000001261
- Moyce, S., Joseph, J., Tancredi, D., Mitchell, D., & Schenker, M. (2016). Cumulative incidence of acute kidney injury in California's agricultural workers. *Journal of Occupational and Environmental Medicine*, 58, 391-397.
- Murray, K. O., Fischer, R. S., Chavarria, D., Duttman, C., Garcia, M. N., Gorchakov, R., . . . Sheleby, J. (2015). Mesoamerican nephropathy: A neglected tropical disease with an infectious etiology? *Microbes and Infection*, 17, 671-675. doi:10.1016/j.micinf.2015.08.005
- National Health Service. (2016). *Acute kidney injury*. Retrieved from <https://www.nhs.uk/conditions/acute-kidney-injury/>
- O'Donnell, J. K., Tobey, M., Weiner, D. E., Stevens, L. A., Johnson, S., Stringham, P., . . . Brooks, D. R. (2011). Prevalence of and risk factors for chronic kidney disease in rural Nicaragua. *Nephrology Dialysis Transplantation*, 26, 2798-2805. doi:10.1093/ndt/gfq385
- Orantes, C. M., Herrera, R., Almaguer, M., Brizuela, E. G., Hernandez, C. E., Bayarre, H., . . . Castro, B. E. (2011). Chronic kidney disease and associated risk factors in the Bajo Lempa region of El Salvador: Nefrolempa study, 2009. *MEDICC Review*, 13(4), 14-22.
- Orantes, C. M., Herrera, R., Almaguer, M., Brizuela, E. G., Nunez, L., Alvarado, N. P., . . . Orellana, P. (2014). Epidemiology of chronic kidney disease in adults of Salvadoran agricultural communities. *MEDICC Review*, 16(2), 23-30.
- Pan American Health Organization. (2013). *Proposed resolution: Chronic kidney disease in agricultural communities in Central America* (CD52/8). Washington, DC: 52nd Directing Council. Retrieved from <https://www.paho.org/hq/dmdocuments/2013/CD52-8-e.pdf>
- Peraza, S., Wesseling, C., Aragon, A., Leiva, R., Garcia-Trabanino, R. A., Torres, C., . . . Hogstedt, C. (2012). Decreased kidney function among agricultural workers in El Salvador. *American Journal of Kidney Diseases*, 59, 531-540. doi:10.1053/j.ajkd.2011.11.039
- Raines, N., Gonzalez, M., Wyatt, C., Kurzrok, M., Pool, C., Lemma, T., . . . Sheffield, P. (2014). Risk factors for reduced glomerular filtration rate in a Nicaraguan community affected by Mesoamerican nephropathy. *MEDICC Review*, 16(2), 16-22.
- Ramirez-Rubio, O., Amador, J. J., Kaufman, J. S., Weiner, D. E., Parikh, C. R., Khan, U., . . . Brooks, D. R. (2016). Urine biomarkers of kidney injury among adolescents in Nicaragua, a region affected by an epidemic of chronic kidney disease of unknown aetiology. *Nephrology Dialysis Transplantation*, 31, 424-432. doi:10.1093/ndt/gfv292
- Ramirez-Rubio, O., Brooks, D. R., Amador, J. J., Kaufman, J. S., Weiner, D. E., & Scammell, M. K. (2013). Chronic kidney disease in Nicaragua: A qualitative analysis of semi-structured interviews with physicians and pharmacists. *BMC Public Health*, 13, Article 350. doi:10.1186/1471-2458-13-350
- Riefkohl, A., Ramirez-Rubio, O., Laws, R. L., McClean, M. D., Weiner, D. E., Kaufman, J. S., . . . Brooks, D. R. (2017). Leptospira seropositivity as a risk factor for Mesoamerican nephropathy. *International Journal of Occupational and Environmental Health*, 23(1), 1-10. doi:10.1080/10773525.2016.1275462
- Roncal Jimenez, C. A., Ishimoto, T., Lanaspá, M. A., Rivard, C. J., Nakagawa, T., Ejaz, A. A., . . . Johnson, R. J. (2014). Fructokinase activity mediates dehydration-induced renal injury. *Kidney International*, 86, 294-302. doi:10.1038/ki.2013.492
- Sanoff, S. L., Callejas, L., Alonso, C. D., Hu, Y., Colindres, R. E., Chin, H., . . . Hogan, S. L. (2010). Positive association of renal insufficiency with agriculture employment and unregulated alcohol consumption in Nicaragua. *Renal Failure*, 32, 766-777. doi:10.3109/0886022x.2010.494333
- Torres, C., Aragon, A., Gonzalez, M., Lopez, I., Jakobsson, K., Elinder, C. G., . . . Wesseling, C. (2010). Decreased kidney function of unknown cause in Nicaragua: A community-based survey. *American Journal of Kidney Diseases*, 55, 485-496. doi:10.1053/j.ajkd.2009.12.012
- Trabanino, R. G., Aguilar, R., Silva, C. R., Mercado, M. O., & Merino, R. L. (2002). [End-stage renal disease among patients in a referral hospital in El Salvador]. *Revista Panamericana de Salud Pública*, 12, 202-206.
- VanDervort, D. R., Lopez, D. L., Orantes, C. M., & Rodriguez, D. S. (2014). Spatial distribution of unspecified chronic kidney disease in El Salvador by crop area cultivated and ambient temperature. *MEDICC Review*, 16(2), 31-38.
- Wegman, D. H., Apelqvist, J., Bottai, M., Ekstrom, U., Garcia-Trabanino, R., Glaser, J., . . . Bodin, T. (2018). Intervention to diminish dehydration and kidney damage among sugarcane workers. *Scandinavian Journal of Work, Environment & Health*, 44, 16-24. doi:10.5271/sjweh.3659
- Wesseling, C., Aragon, A., Gonzalez, M., Weiss, I., Glaser, J., Bobadilla, N. A., . . . Barregard, L. (2016). Kidney function in sugarcane cutters in Nicaragua—A longitudinal study of workers at risk of Mesoamerican nephropathy. *Environmental Research*, 147, 125-132. doi:10.1016/j.envres.2016.02.002
- Wesseling, C., Aragon, A., Gonzalez, M., Weiss, I., Glaser, J., Rivard, C. J., . . . Johnson, R. J. (2016). Heat stress, hydration and uric acid: A cross-sectional study in workers of three occupations in a hotspot of Mesoamerican nephropathy in Nicaragua. *BMJ Open*, 6(12), e011034. doi:10.1136/bmjopen-2016-011034
- Wesseling, C., Crowe, J., Hogstedt, C., Jakobsson, K., Lucas, R., & Wegman, D. H. (2014). Resolving the enigma of the mesoamerican nephropathy: A research workshop summary. *American Journal of Kidney Diseases*, 63, 396-404. doi:10.1053/j.ajkd.2013.08.014
- Wesseling, C., van Wendel de Joode, B., Crowe, J., Rittner, R., Sanati, N. A., Hogstedt, C., & Jakobsson, K. (2015). Mesoamerican nephropathy: Geographical distribution and time trends of chronic kidney disease

mortality between 1970 and 2012 in Costa Rica. *Occupational and Environmental Medicine*, 72, 714-721. doi:10.1136/oemed-2014-102799

Wijkstrom, J., Leiva, R., Elinder, C. G., Leiva, S., Trujillo, Z., Trujillo, L., . . . Wernerson, A. (2013). Clinical and pathological characterization of Mesoamerican nephropathy: A new kidney disease in Central America. *American Journal of Kidney Diseases*, 62, 908-918. doi:10.1053/j.ajkd.2013.05.019

Yang, C. W. (2018). Leptospirosis renal disease: Emerging culprit of chronic kidney disease unknown etiology. *Nephron*, 138, 129-136. doi:10.1159/000480691

Author Biographies

Roxana Chicas, BSN, RN, is a PhD candidate at Nell Hodgson Woodruff School of Nursing. Her research focuses on occupational and environmental health, and work safety interventions.

Jacqueline Mix is an adjunct professor at Nell Hodgson Woodruff School of Nursing. Her research is primarily focused in the areas of environmental and cancer epidemiology.

Valerie Mac, PhD, FNP-C is an assistant professor at Nell Hodgson Woodruff School of Nursing. Her research focuses on

biomonitoring and the health effects of heat in vulnerable and occupational populations.

Joan Flocks is the Director of the Social Policy Division at the Center for Governmental Responsibility (CGR), University of Florida Levin College of Law. She teaches courses and publishes in the areas of social and environmental justice.

Nathan Eric Dickman is an associate professor of philosophy and religious studies at Young Harris College. He researches and teaches about global social justice issues in ethic and religions.

Vicki Hertzberg is a professor and the Director of the Center for Data Science in the Nell Hodgson Woodruff School of Nursing. Her research focuses on developing and applying statistical methods for the analysis of network data.

Linda McCauley is dean and professor at Nell Hodgson Woodruff School of Nursing. Her research focuses on occupational and environmental studies of working populations and children.