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Chronic Kidney Disease from Non-Traditional Causes throughout Central America

Abigail K. Watson
University of South Carolina - Columbia

Director of Thesis: Myriam Torres
Second Reader: Dr. Edena Guimaraes

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I. ABSTRACT

Throughout many Central American countries, incidence of chronic kidney disease (CKD) has been on the rise. The disease mainly affects agricultural workers and differs from typical CKD. Patients in these countries often do not have preexisting conditions such as diabetes or hypertension known to be traditional causes of CKD. They also experience increased damage to the kidney tubules, rather than the glomeruli generally more heavily impacted. There has been speculation regarding the causes of CKDnT (chronic kidney disease of nontraditional causes), but no consensus has been reached. Two major hypotheses to explain the high prevalence among Central American sugarcane workers are patterns of cyclical dehydration throughout the work shift, and exposure to agrochemicals. While dehydration-induced damage is the favored hypothesis at this time, other factors cannot be eliminated without further research.

In order to reduce the incidence of CKDnT among sugarcane workers, certain policies could be established. First, shaded break areas and more break time allotted throughout the work day would help lower the body temperatures of workers. Secondly, masks and protective clothing should be required or, at the least, more highly regulated in order to reduce agrochemical exposure. Programs such as that led by the Caja Costarricense Seguro Social should continue to educate all citizens about the importance of drinking water.

II. INSPIRATION FOR THESIS TOPIC

In May of 2018, I travelled to Costa Rica with 21 students and 4 faculty members from the University of South Carolina. The trip was a Global Health study abroad program based in San José, Costa Rica. I took classes including Spanish for Healthcare Professionals and Epidemiology. We travelled to various provinces throughout the country learning about the Costa Rican universal healthcare system and volunteering in local schools, nursing homes, and homes for patients living with AIDS. Outside of class-time, we attended lectures and local hospitals, both private and government-run. For example, we visited the private hospital, Clínica Bíblica on May 16, 2018 to tour the facility and receive a lecture on the universal healthcare system from Dr. Rodolfo Garbanzo. This was followed by another lecture form Dr. Avendaño on May 24. On this same day, we visited a primary healthcare clinic commonly referred to as an EBAIS, Equipos Básicos de Atención Integral en Salud. We were fortunate to speak with staff members on the clinics' roles in Costa Rican healthcare, and able to compare these to the larger clinic, Clínica Tibás which we visited no May 29.

The major inspiration for my project came from the trips to a high school and elementary school in Guanacaste on May 21 and May 22, respectively. Our trip partnered with the Caja Costarricense de Seguro Social, the public health sector of Costa Rica, in order to educate the students on the importance of drinking water. The original concept seemed simple to me, as a citizen of the United States who is able to drink from most any faucet. While its beaches have attracted an economy for tourism, inland Guanacaste has some of the highest rates of poverty and unemployment in Costa Rica. It is not uncommon for households to lack running, potable water. The program with the Caja Costarricense de Seguro Social focused on the importance of drinking water for its contribution to kidney health. More difficult access to drinkable water

coupled with high heat, only exacerbated by climate change, has contributed to elevated rates of chronic kidney disease.

Taking my first-ever epidemiology course while abroad, I decided to combine the knowledge from my course with the first-hand experience I gained while working with the Caja Costarricense de Seguro Social to compile comprehensive documentation of the epidemiology of and educational efforts behind chronic kidney disease throughout Pan-American countries, with emphasis on Costa Rica. I have used primary research, as well as reviews of studies to detail the epidemiological spread, while also considering the educational and regulatory efforts currently in place to reduce incidence of chronic kidney disease.

III. CHRONIC KIDNEY DISEASE

Chronic kidney disease (CKD) results from lasting kidney damage which inhibits a patient's kidneys from proper functioning. The kidney's main functions are to filter minerals, wastes, and molecules from the blood for urine formation and maintain fluid balance. According to the National Kidney Foundation, the disease is the 18th most common killer worldwide.

First signs of kidney disease often do not appear until the kidneys are badly damaged. Symptoms may include, but are not limited to muscle cramping, nausea, loss of appetite, changes in urinary frequency, and edema of lower extremities (American Kidney Fund). Chronic kidney disease begins in 5 stages, with Stage 1 representing mild damage and Stage 5 indicating kidney failure. Each stage is generally characterized by the estimated glomerular filtration rate (eGFR) of the kidneys. The glomerulus is a bundle of capillary vessels which begins the filtration process of plasma in the nephrons. A healthy kidney should have an eGFR of 90 ml/min/1.73 m^2 or higher. The 5 Stages of CKD are as follows:

Stage 1: eGFR of 90 ml/min/1.73 m^2 or higher, but other signs of damage, most commonly proteinuria, are present

Stage 2: eGFR between 60 and 89 ml/min/1.73 m^2 with other signs of damage, such as proteinuria or physical damage to the kidneys.

Stage 3: eGFR between 30 and 59 ml/min/1.73 m^2 indicating moderate kidney damage. Symptoms at Stage 3, if existent, are fairly mild such as edema or back pain.

Stage 4: eGFR between 15 and 29 ml/min/1.73 m^2 indicating severe damage. Symptoms may also include changes in urinary frequency.

Stage 5: eGFR >15 ml/min/1.73 m^2 indicating kidney failure

Another method of measuring renal disease is measuring blood serum creatinine levels. Creatinine is a waste product resulting from muscle activity which is filtered out of the blood by functioning kidneys. A damaged kidney will be unable to filter the creatinine, therefore resulting in an elevated serum creatinine level. Normal serum creatinine levels range from 0.6–1.1 mg/dL in women and 0.7–1.3 mg/dL in men.

Once a patient reaches Stage 5 with kidney failure, treatment options include dialysis or transplantation. Dialysis is a method for filtering the blood when the kidneys cannot perform this job themselves. Though the most common method, only 35% of dialysis patients survive for 5 years of treatment (UCSF Medical Center, 2018). Kidney transplant is the most reliable current treatment method, though it requires surgery and a lifetime of immunosuppressant prescription medication.

End-stage renal disease affects nearly 2 million people worldwide, and this number continues to increase by about 5-7% every year (UCSF Medical Center, 2018). The number of patients waiting for donor kidneys increases by about 8% per year, but the supply of deceased or living donors has remained nearly constant.

Patients with diabetes mellitus, hypertension, cardiovascular disease, or obesity are at higher risk for developing chronic kidney disease. These conditions put excess strain on the glomeruli, resulting in scarring and damage as depicted in Figure 1.

Figure 1: Healthy Kidney (left) compared to a Damaged Kidney (right)

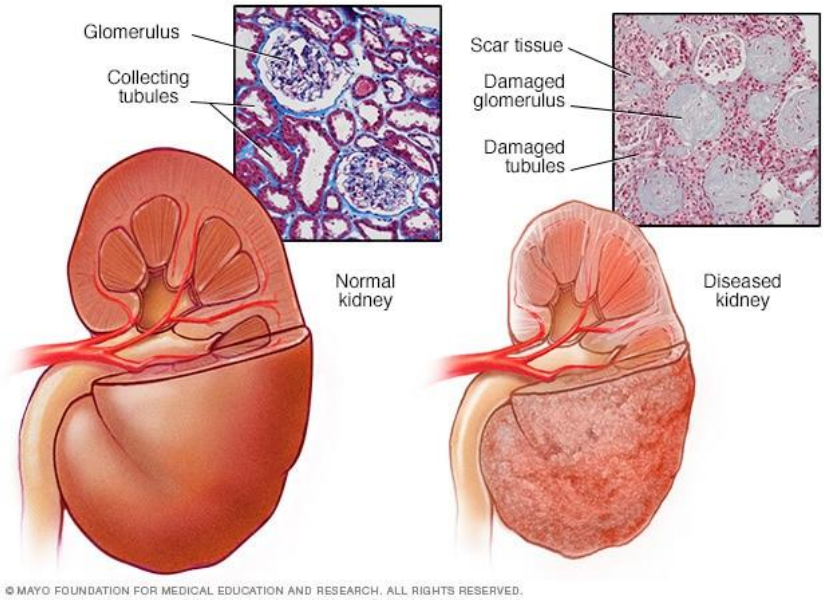

Figure 1: Chronic kidney disease mainly affects the glomeruli, negatively affecting the filtration capabilities of the kidney. The damage and scarring is visible in the glomeruli and tubules with surrounding scar tissue (Mayo Clinic Staff, 2019).

IV. CKD IN MESOAMERICAN COUNTRIES

Beginning in the 1970s, cases of chronic kidney disease riddled Central American countries. The disease was different than is typically observed in wealthier countries. Instead of damaging the filtering system of the kidneys, most patients in Central American countries showed damage to the kidney tubules. The proximal convoluted tubules of the kidneys function in the reabsorption of water, glucose, amino acids, and ions, whereas the and distal convoluted tubules function to secrete waste and ions. It has been shown that the severity and frequency of acute kidney injuries (AKI) to the tubules are directly correlated to the progression of CKD (Takaori, 2016). Chronic kidney disease is usually characterized by preexisting conditions such as diabetes or hypertension, but this is not the case in many Central American patients. One study on CKD in rural Nicaragua showed that 92% of participants did not have diabetes, and 64% had never had hypertension, indicating that 57-64% of CKD participants were experiencing CKD of nontraditional causes (CKDnT) (Lozier, 2016). By 2013, the Pan American Health Organization, the U.S. Centers for Disease Control and Prevention, and the Latin American Society of Nephrology and Hypertension worked to create surveillance program for CKDnT to gain knowledge on the epidemic (Ferreiro, 2016).

The first case of CKDnT in Central America wasn't documented until 2002, but it is estimated to have been silently prevalent for decades prior. According to a report published in the *Tico Times*, a Costa Rican newspaper, 10% of CKD cases worldwide are of unknown causes (Fendt, 2015). In El Salvador, however, the prevalence of CKDnT nears 28% in men and 14% in women, and in high-risk areas of Nicaragua, the prevalence is 20% in men and 8% in women. The overall presence of CKDnT is more common among men than women in a ratio of about 4:1.17 (Méndez-Chacón, 2016).

CKDnT is generally asymptomatic in its early stages, so damage is severe by the time patients seek help. Patients generally present with elevated serum creatinine levels and reduced glomerular filtration rates, but little to no proteinuria (Zoccali, 2017). Biopsies have revealed tubulointerstitial nephritis (tubular damage) with glomerulosclerosis (hardening due to scars of the blood vessels in the glomeruli) and ischemia (reduced blood flow) of the kidneys (Ramirez-Rubio, 2013). An estimated 20,000 people have died prematurely due to the epidemic (Ramirez-Rubio, 2013). Compared to the United States of America at 4 per 100,000 people, the crude mortality rates of CKD in Costa Rica are nearly three times higher at 11.48 per 100,000 (Méndez-Chacón, 2016). Significantly higher still in Nicaragua and El Salvador, mortality rates reach 66 and 64 per 100,000, respectively (Lozier 2016). Rates vary throughout the countries' regions and populations. For example, the mortality rate in Guanacaste, Costa Rica has increased from 20.3 to 38.23 per 100,000 between 1990 to 2011 (Méndez-Chacón, 2016). The average age of onset in Guanacaste, 30-34 years, is also about 20 years younger than the national average (Méndez-Chacón, 2016). The early-age diagnoses present a high social cost due to the long duration of treatments. Countries such as Costa Rica with universal healthcare are therefore presented with high social costs. Renal replacement therapies cost about $23,000 per year and are covered entirely by the Costa Rican social security fund for healthcare (Cerdas, 2015). Latin America overall had 119 patients per million population (pmp) with end-stage renal disease undergoing renal preplacement therapy in 1991. By 2010, these numbers had increased to 660 pmp, (Gonzalez-Bedat, 2015). In Costa Rica in 2002, kidney transplants occurred at 24.81 pmp costing the government $6,000 USD for the initial transplant, $7,538 for the first year, and $3,032 every year after (Cerdas, 2015). Costa Rica has one of the most highly ranked health systems in the world, at number 37 just above the United States ranked number 38 according to

the World Health Organization. Still, kidney dialysis centers are scarce—only 4 exist, all located in the capital city of San José (Cerdas, 2015). It is still estimated that CKD is underdiagnosed in many Central American countries. Although incidence of CKD throughout Central America is found to be increasing, this could be due to new educational efforts leading to earlier detection, and better diagnosis methods of the disease. Still, between 2005 and 2016, the Pan American Health Organization's reports a 35.5% increase in years of potential life lost due to kidney disease in Costa Rica (Health in the Americas, 2017).

Multiple hypotheses exist to predict the causes of elevated levels of CKDnT in Central American countries. Given the heavily affected population of males between the ages of 20-40 years old working in agriculture, major factors are estimated to be agrochemical exposure (both on the job and in water supplies of surrounding areas) and cyclical patterns of dehydration causing acute kidney injury during work shifts. The latter hypothesis seems to be the most supported, but no factors can be ruled out given the current level of existing research.

V. CKD AMONG AGRICULTURAL WORKERS

Elevated levels of chronic kidney disease (CKD) have been appearing among agricultural workers. These cases are due to nontraditional causes (cases are unrelated to diabetes mellitus, hypertension, aging, etc.), and are expected to be related to environmental factors. High heat throughout the agricultural fields coupled with low water intake puts Pan American field workers at high risk of developing chronic kidney disease of nontraditional causes (CKDnT).

MESOAMERICAN NEPHROPATHY

The term Mesoamerican nephropathy arose from the findings that, beginning in the 1970s, increased incidence of chronic kidney disease were troubling young sugarcane workers throughout the Central American Pacific Coast (Johnson, 2019). In 2015, for example, the incidence of CKD at one major Nicaraguan region was 239 per 100,000 agricultural workers (Fischer, 2018). Between 2005 and 2011, incidence of CKD rose 26%, becoming the 2nd largest killer of men in the country (Storr, 2012). While most prevalent among sugarcane workers in the low altitude fields, cotton and corn farmers, as well as construction workers and miners, have been experiencing increasing levels of CKDnT. It is estimated that acute Mesoamerican nephropathy develops into CKD in about 10.8% of fieldworkers, and the transition generally only takes about 6 months after the appearance of the first clinical signs (Fischer, 2018). Determining clinical features of Mesoamerican nephropathy can increase early detection of the condition to reduce morbidity and mortality from untreated or mistreated renal diseases in Central America.

Three major factors that are thought to contribute to Mesoamerican nephropathy are heat-associated dehydration, exposure to pesticides and toxins, and infectious agents, as outlined in Figure 2.

Figure 2: Possible Mechanisms for the Development of Mesoamerican Nephropathy

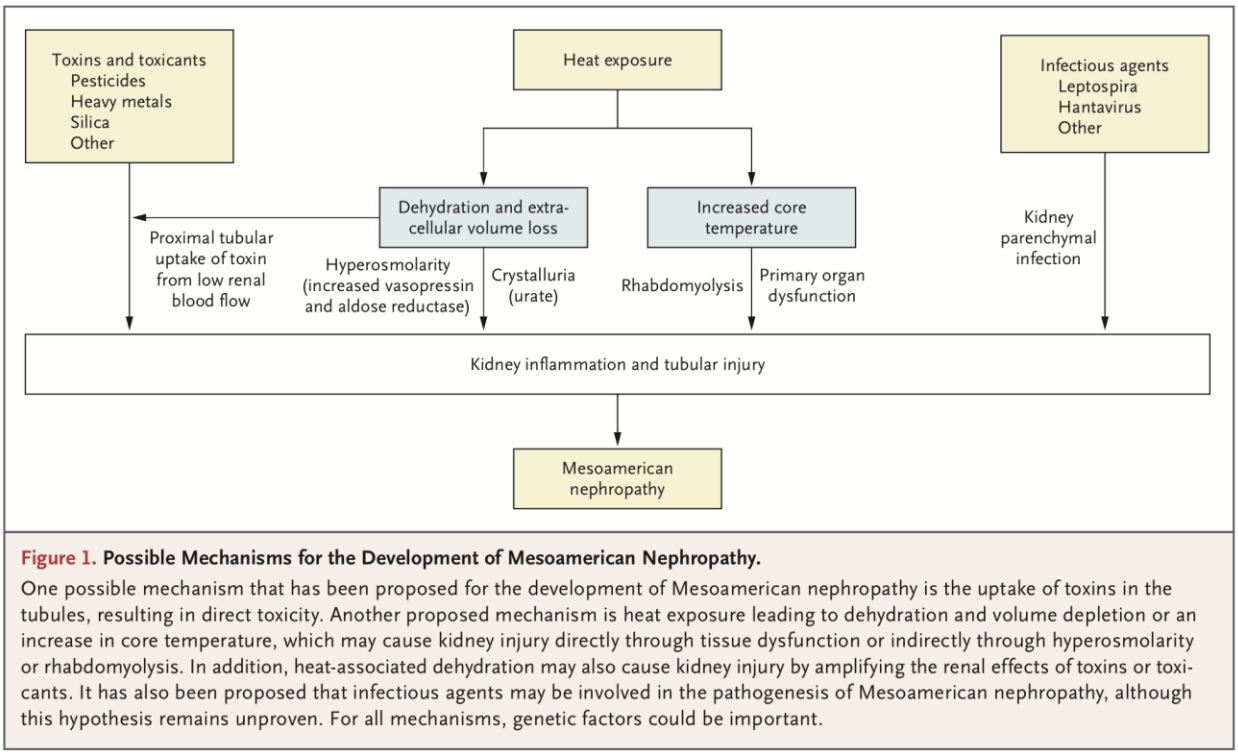

Figure 1. Possible Mechanisms for the Development of Mesoamerican Nephropathy.
One possible mechanism that has been proposed for the development of Mesoamerican nephropathy is the uptake of toxins in the tubules, resulting in direct toxicity. Another proposed mechanism is heat exposure leading to dehydration and volume depletion or an increase in core temperature, which may cause kidney injury directly through tissue dysfunction or indirectly through hyperosmolarity or rhabdomyolysis. In addition, heat-associated dehydration may also cause kidney injury by amplifying the renal effects of toxins or toxicants. It has also been proposed that infectious agents may be involved in the pathogenesis of Mesoamerican nephropathy, although this hypothesis remains unproven. For all mechanisms, genetic factors could be important.

Figure 2: The causes of Mesoamerican nephropathy, though greatly unknown, are believed to result mainly from exposure to agrochemicals, heat, or infectious agents (Johnson, 2019).

According to a review article, Johnson (2019), Mesoamerican nephropathy among agricultural workers has multiple potentially contributing factors. One major hypothesis is that daily repetition of acute damage to workers' kidneys can predispose patients to CKD. Support for this hypothesis comes from studies showing patterns of severe dehydration influence chronic kidney disease formation in rats (Robey, 2014). Agricultural workers in Mesoamerican countries

were found to have increasing serum creatinine levels throughout each field shift (Johnson, 2019). Serum creatinine levels, as described in Section III, are an indicator of kidney function.

A 2014-2015 study published in the American Journal of Kidney Disease compared the serum creatinine levels of 326 Nicaraguan sugar-cane workers with no history of CKD from pre-harvest and post-harvest season. The average pre-harvest season levels of creatinine were measured to be 1.01 mg/dL. Development of acute kidney injury (AKI) throughout the study was defined as an increase of at least 0.3 mg/dL to a serum creatinine level of 1.3 mg/dL or higher by the end of the harvest season. Thirty-four, or 10.4% of participants developed AKI during the single harvest season with an average serum creatinine of 1.64 mg/dL. Twenty-nine of these patients completed a follow-up study 6 months later in which researchers measured the regeneration of workers' kidney function during the off-season. The process of participant enrollment in the follow-up study is outlined in Figure 3.

Figure 3: Participant Enrollment Outline for 2014-15 Study on Acute Kidney Injury

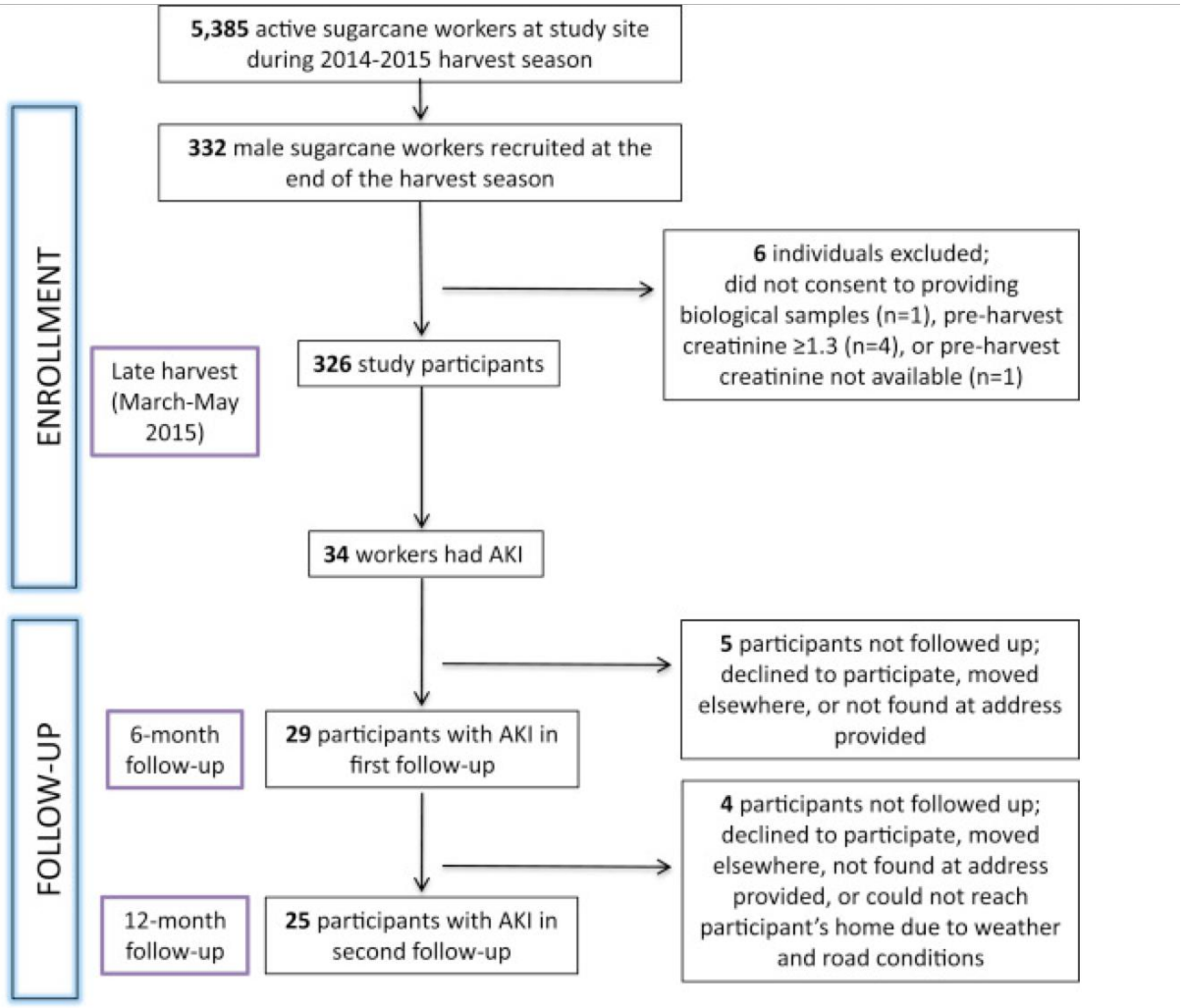

Figure 3: Study participants outlined as shown above detailing the participation of 326 sugarcane workers enrolled in the study, 34 developing AKI, and 6 and 12 month follow ups with 29, then 24 of these patients (Kupferman, 2018).

Six months after the harvest season, average serum creatinine levels had dropped from 1.64 mg/dL to 1.25 mg/dL among participants. There was no significant difference between serum creatinine levels from 6 months to 12 months. Results of the longitudinal follow-up study

are outlined in Figure 4 below. While 34 participants were included in the initial serum creatinine level readings, 29 remained at the 6 month follow-up, and 24 participants at the 12 month.

Figure 4: Serum Creatinine Levels at Baseline compared with Follow-up in 2014-15 Study on Acute Kidney Injury

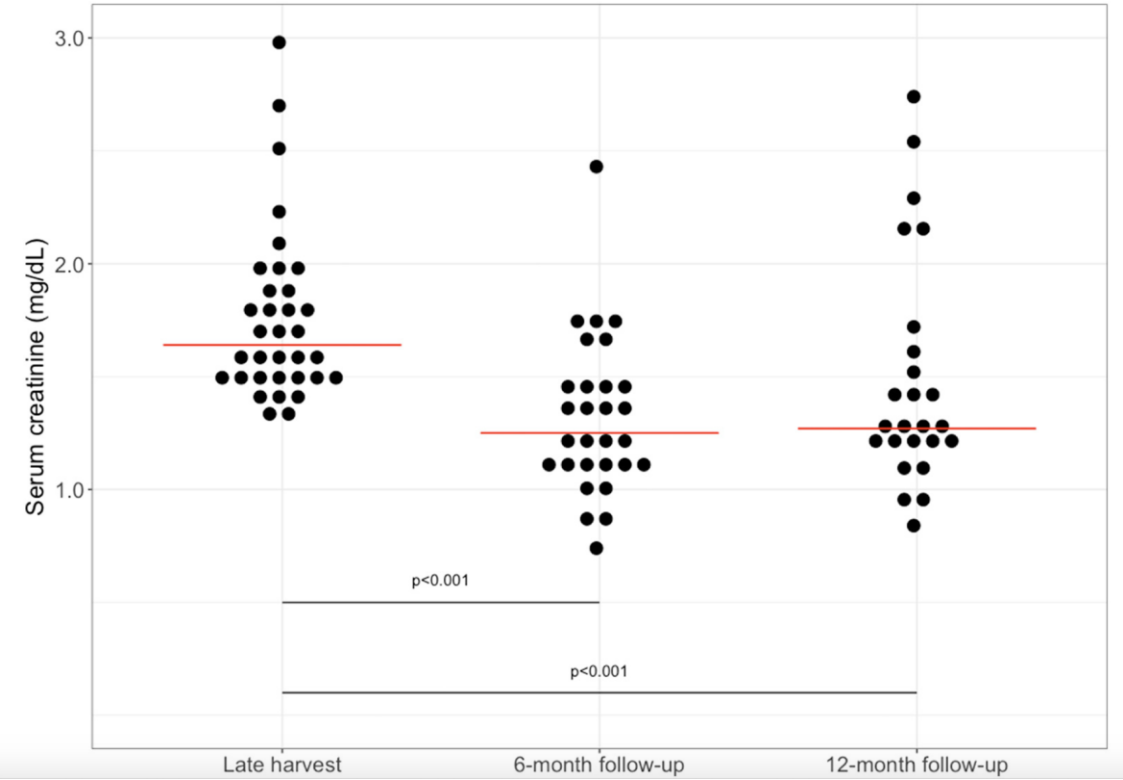

Figure 4: Serum creatinine levels were shown to decrease from an average of 1.64 mg/dL at the end of harvest season to averages of 1.25 mg/dL and 1.27 mg/dL after a 6- and 12-month rest period, respectively (Kupferman, 2018).

This finding supports the hypothesis that kidneys obtain acute damage throughout harvest seasons. Damage can be diminished after a period of rest, though the rest period may not fully

restore kidneys to pre-harvest serum creatinine levels. While the transition from AKI to CKD is unknown, the researchers' hypothesis questions whether repeated cycles of damage can accumulate into the chronic form of kidney disease. The sugarcane workers in this study experienced partial regeneration of kidney function if they discontinued field work, but more than 1/3 of the participants who experienced any AKI during the harvest season maintained a greater than 30% decrease in estimated glomerular filtration rate (eGFR). The glomerular filtration rate is a measure of how much blood passes through glomeruli (which filter waste from the blood) per minute and gives a strong indication of kidney function. At the 12-month check-up, the 24 remaining participants averaged less than 60 ml/min/1.73 m^2. According to the National Kidney Foundation, a normal eGFR for adults is at least 90 ml/min/1.73 m^2. One sign of chronic kidney disease is an eGFR reading of less than 60 ml/min/1.73 m^2 for 3 consecutive months (National Kidney Foundation, 2019). A single reading of decreased eGFR indicates loss of kidney function.

The exact cause of these increased serum creatinine levels and decreased eGFR measurements could come from multiple factors, such as heat-associated dehydration, agrochemical exposure, infectious agents, altitude, genetic factors, or a confluence of contributors. A couple potential causes in Mesoamerican agricultural workers are detailed below.

MESOAMERICAN NEPHROPATHY AND HEAT

Excessive heat in the Mesoamerican region contributes to dehydration, especially among agricultural workers who spend a majority of the day in the sun. To examine the effects of heat-related dehydration kidney health, researchers led by García-Trabanino (2015) examined 189 (168 male, 21 female) El Salvadorian sugarcane workers before and after their daily shifts in the

field. Participants were 18-49 years of age (averaging 30 years) who worked a daily average of 4 hours (ranging from 1.4-11 hours). Average temperatures for the workdays were 34-36 °C (93.2-96.8 °F) before 12 PM, and 39-42 °C (102.2-109.4 °F) after noon. Most participants worked from about 5:30 AM-12 PM, but some worked as late as 4 PM. Characteristics of the participants are outlined in further detail in Table 1 below. One interesting factor to notice is the pesticide exposure among 89% of participants, creating a confounding factor which will be investigated further in the next section.

Table 1: Characteristics of 189 El Salvadorian sugarcane-worker participants

Sex, N men/women	168/21
Age, years (mean)	30 (18–49)
Body weight, pre-shift, kg (mean)	64 (45–108)
Men	65 (45–108)
Women[a]	60 (48–79)
Height, cm (mean)	164 (140–182)
BMI	24 (18–36)
Men	23 (18–36)
Women[a]	25
Current smokers (%)	28
Ex-smokers (%)	23
Alcohol≥7 drinks/week (%)	5
Literate (%)	79
Previous harvests, N (range)	9 (1–38)
Ever used pesticides (%)[b]	89

Table 1: Characteristics of 189 study participants to detail effects of cyclical heat-induced dehydration on kidney health (García-Trabanino, 2015).

Average water intake throughout the days was 0.8 L per hour. According to the Occupational Health and Safety Administration through the United States Department of Labor, workers in the heat should be consuming between 1.0-1.4 L of water per hour. The mean 0.8 L of water consumed per hour was enough to maintain the body weight of workers, but not enough to protect the kidneys from reduced glomerular filtration and stressful tubular reabsorption.

Results of the study showed high prevalence of lowered kidney function among the El Salvadorian sugarcane workers. During one workday, 14% of male participants experienced an eGFR reduced to a rate less than 60 mL/min. Most likely secondary to reduced GFR, participants showed an about 10% increase in serum creatinine, urea nitrogen, and uric acid from the beginning to the end of the work shift. Decreased blood flow and pressure through the kidneys could result in a lower elimination of these wastes within workers' urine. The most notable finding was the increase in workers with elevated serum uric acid levels. Before the shifts, 26% of participants showed elevated serum uric acid levels, whereas elevated levels were prevalent among 43% of participants post-shift. The pattern by which cyclical dehydration could induce repeated kidney damage is outlined in Figure 5.

Figure 5: Method by which repeated Acute Kidney Injury could invoke Chronic Kidney Disease

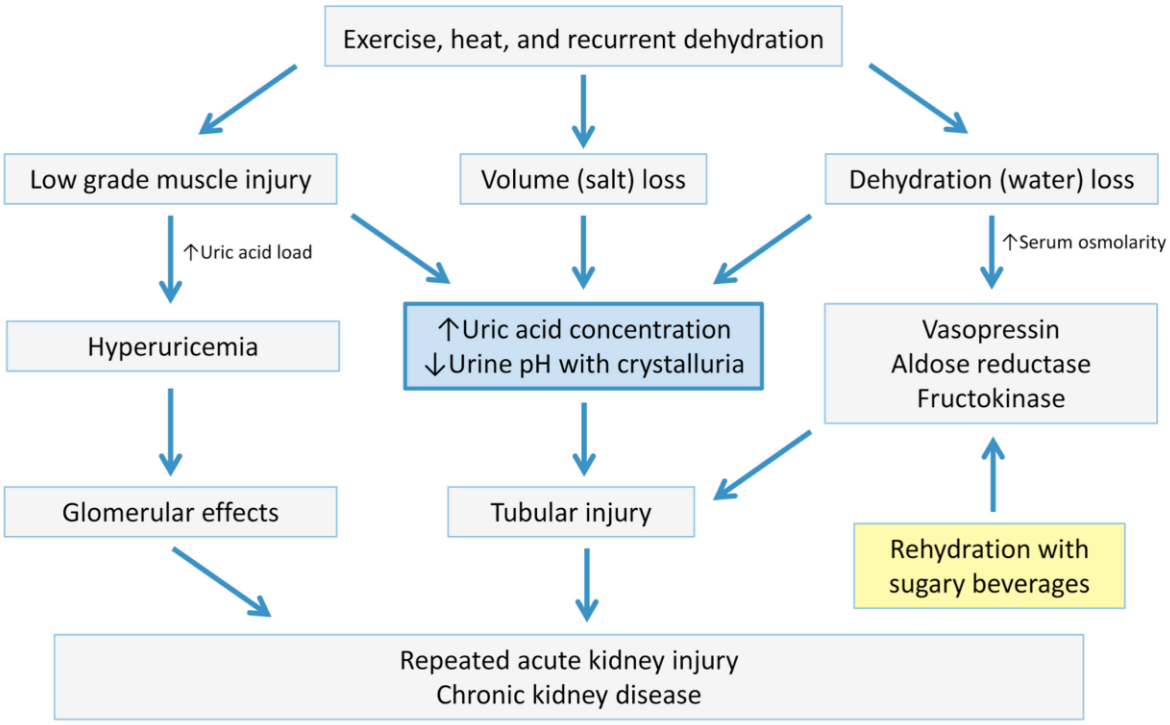

Figure 5: Potential factors resulting in CKDnT observed among Central Americans, namely sugarcane workers (García-Trabanino, 2015).

Aldosterone, which increases blood volume and pressure by enhancing the reabsorption of sodium and water through the distal convoluted tubule, as well as lactate, produced through anaerobic respiration during the long workday, decrease the pH of urine. Combining the effects of concentrated, acidic urine and elevated serum uric acid levels can increase the formation of urate crystals. According to another study performed by Roncal-Jimenez (2015), hyperuricemia and uricosuria (elevated uric acid levels in the blood and urine, respectively, contribute to the development of Mesoamerican nephropathy. Elevated urinary uric acid levels, which were present at the end of the workday, can result in direct injury to renal tubules. In the general

population, urine pH is about 5.9-6.0, but over 80% of Costa Rican sugarcane workers had a urine pH less than 5 by the end of their workday shift (Roncal-Jimenez, 2015). As urine pH increases, uric acid solubility decreases, thus contributing to crystalluria. These urate crystals induce inflammation and damage of the kidney tubules commonly observed in patients with CKD.

MESOAMERICAN NEPHROPATHY AND PESTICIDES

Heat stress and dehydration among sugarcane workers in Mesoamerica combined with pesticide usage may contribute to the CKD of nontraditional causes epidemic in Central American countries. No direct connection between pesticides and CKD can be confirmed, but it is notable that many Central American countries rank among the highest users of highly toxic pesticides in the world. Imports of active toxins for agrochemicals increased by 33% between 2000-2004 (Ordunez, 2014). Costa Rica, according to 2008 national statistics, experiences approximately 100 fatal and 200 acute cases of pesticide poisoning each year. The toxins have invaded groundwater, wells, and coastal areas, putting the population at large at risk. Drinking water in parts of Guanacaste has been shown to contain 13 times more arsenic than is deemed safe by the World Health Organization (Fendt, 2015). Guanacaste has the highest rates of CKD in Costa Rica, at 18-20 times other provinces (Fendt, 2015). Though arsenic has never been directly linked with kidney disease, it provides evidence that other toxins may be present in water sources as well.

Central American countries have a long-documented mishandling of agricultural toxins (Wesseling, 2005). Considering the fact that CKD of nontraditional causes is “virtually absent” in other sugarcane cultivating countries with similar climates, Carlos-Silva (2014) suggests that

heat and cyclical dehydration patterns alone cannot accurately describe the causes of Mesoamerican nephropathy (Carlos-Silva, 2014).

In the study led by Ramón García-Trabanino (2015) outlined in MESOAMERICAN NEPHROPATHY AND HEAT, 89% of El Salvadoran sugarcane worker participants reported pesticide use. Of the 23 workers who were found to have a reduced eGFR throughout the study, 74% reported carbamate pesticide usage, whereas 29% of participants without elevated eGFRs reported use of carbamate pesticides.

A.K. Tripathi (2016) conducted a study to determine if blood levels of organochlorine pesticides correlated directly with the development of CKD from nontraditional causes. Organochlorine pesticides are widely used in Indian agricultural fields and have become a major pollutant of India. The study compared 3 groups of subjects: healthy peoples, patients with CKD of nontraditional causes, and patients with CKD of known etiology. Participants were tested for blood levels of organochlorine pesticides and cellular oxidative stress. NADPH oxidase and TGF-β expression were used as indicators of oxidative stress. Participants with CKD of unknown etiology had significantly elevated blood organochlorine levels when compared with the healthy and traditional CKD patients. The blood organochlorine levels in the participants with CKD of nontraditional causes were significantly correlated with the patients' eGFR. The pesticides were found to increase oxidative stress by inducing mRNA and protein expression of NADPH oxidase and TGF-β, indicating one possible method by which organochlorine pesticides can increase risk for developing CKD. While this study was conducted in India rather than Central America, the results are applicable to potential contributing factors for Mesoamerican nephropathy and should be further investigated.

One herbicide commonly used in Costa Rican fields is a yellow mixture of amine, atrazine, 2,4-Dichlorophenoxyacetic acid (2,4-D), pendimethalin, and terbutryn (Storr, 2012). According to an authority of agrochemical health at the University of Sterling, Andrew Watterson, high levels of atrazine can damage kidneys, acute exposure to 2,4-D can lead to chronic kidney damage and feeding terbutryn to rats in a lab setting results in kidney damage (Storr, 2012). While none of the chemicals were singly toxic, exposure to all 5 in stressful climates could worsen the effects.

REDUCING MESOAMERICAN NEPHROPATHY

Studies listed above monitored the drinks typically consumed by sugarcane workers throughout the workday. While 90% of drinks were water, the last 10% was mainly composed of sugary drinks. Reducing the consumption of sugary drinks throughout the workday and increasing water intake are the most obvious ways to limit the effects of cyclical heat-induced dehydration. Along with increased water, consumption, however, sugarcane workers should be advised to consume salt or foods with sodium. The sodium allows the water to be reabsorbed from the kidneys and remain in the blood stream to maintain blood pressure and allow the kidneys to filter the blood properly.

It was reported during the various studies that many of the sugarcane workers took limited breaks, and this breaktime was rarely spent in shaded areas. Work places should increase access to shade to allow workers cooler places to sit and relax during long daytime shifts. According to the United States Occupational Safety and Health Administration, OSHA, rest time should account for 50% of worktime when temperatures rise beyond 28 °C (82.4 °F), and 75% of the time when temperatures exceed 30 °C (86°F) to maintain a typical core body temperature

(García-Trabanino, 2015). The studies performed occurred under direct sunlight in heat that typically ranged between 34-42 °C. This type of heat can only be counteracted by sweating. The act of sweating contributes to dehydration, though this is limited by the fact that many of the participants work in long shirts and pants to avoid sunlight.

One final potential protective measure against Mesoamerican nephropathy for sugarcane workers is proper masks and protection from pesticide exposure. According to 37-year-old Omar Rojas, a person responsible for paying the pesticide sprayers, purchasing safety gear is "up to everyone individually. There are recommendations on all the chemicals, but nobody regulates it," (Storr, 2012). Enacting regulatory efforts to ensure proper clothing and mask protection during sprays or requiring companies to supply the materials to workers could reduce sprayer exposure. In order to limit the toxins from spreading through groundwater to drinking sources, wells must be properly sited and monitored to reduce exposure to chemicals. If contamination occurs, it should be contained to prevent migration, and water should be treated before being returned to the aquifer (Getting up to Speed, 2015). These solutions can be time-consuming, so a quick alternative is to purchase bottled water. This is an unrealistic long-term solution due to individual expenses.

VI. CONCLUSIONS AND FUTURE IMPROVEMENTS

More research is required to understand the mechanisms that drive the development of CKDnT. The crisis presents severe financial costs for Central American countries, as well as social costs. Since the first documented case in 2002, an estimated 20,000 lives have been prematurely lost chronic kidney disease of nontraditional causes.

Increasing treatment locations and opportunities for currently affected patients is one of the first and most crucial steps in reducing the effects of chronic kidney disease. With just 4 major dialysis centers in Costa Rica, 31 in El Salvador, and 13 nephrologists in Nicaragua in 2010, care cannot extend to all those in need (Alvarez, 2010). Especially considering the fact that a majority of patients with CKDnT live in rural regions of the countries, care centers must be broadened.

In order to prevent future cases, education is the first step. Farmworkers and manual laborers should be warned of the dangers of heat and pesticide exposure. Workers should be encouraged to drink water as opposed to sugary beverages. On especially hot workdays, mandatory breaktime should be implemented and shaded areas should be accessible to the workers. As for agrochemical exposure, regulations on safety equipment must be upheld if masks and protective clothing are not provided by the companies.

Programs for early education, such as that led by the Caja Costarricense de Seguro Social in local schools of Guanacaste, should be expanded upon. Many residents of areas such as Guanacaste are hesitant to drink water in fear of impurities. Encouraging methods of purification and providing bottled water to students instills the habits at a young age. I am honored to have

participated in an event such as those in Guanacaste schools and to meet students with whom I am still in contact.

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