Chronic Kidney Disease in Nicaraguan Sugarcane Workers: A Historical, Medical, Environmental Analysis and Ethical Analysis

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Citation

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Abstract
Over the past two decades, roughly 20,000 people in Central America have died from chronic kidney disease of unknown origins (CKDu).[1] CKDu is growing into an unsolvable epidemic due to the mysterious cause of the disease and the little treatment available in the underdeveloped region. CKDu primarily affects sugarcane workers in Nicaragua and El Salvador, but it has also appeared in the rice paddy fields of Sri Lanka. Researchers from Sri Lanka, Boston University, and University of Colorado have proposed causes for the disease such as the pesticide glyphosate, occupational hazards like heat and dehydration, and sugar consumption, respectively; however disagreements still persist. The goal of this paper is to add to the claims already made so that a clearer hypothesis is formed. The paper will also focus on CKDu in Nicaragua to raise more awareness and to pressure the sugarcane companies into changing the country’s policy. Many aspects of CKDu will be analyzed including a history of sugarcane and pesticide usage, medical information about CKDu and Nicaragua’s treatment of the disease, ethics of the companies, and the environmental impact. The methods used in this research include observations and discussions with former sugarcane workers and their relatives during a two week trip to Nicaragua.

INTRODUCTION
Chronic Kidney Disease of unknown origins (CKDu) has been the cause of death for roughly 20,000 people in only two decades. Although a typically treatable disease, certain factors contribute to the increasing CKDu death toll; factors include conflicting multiple causes, treatment availability, and sugarcane and government policies.

At present, three main theories propose a cause for CKDu presence in Central America, and this paper will propose a fourth one. First, the Ministry of Health in Sri Lanka and El Salvador both argue that the agrochemicals such as glyphosate cause CKDu. Dr. Carlos Orantes, a kidney specialist with El Salvador’s Ministry of Health, names three factors in the development of CKDu: the use of prohibited pesticides, combinations of pesticides, and no protection from pesticides.[2] Second, a Boston University research team contends that “occupational” hazards like dehydration from the extreme heat cause CKDu.[3] The team is also conducting research in genetics and early kidney injury in adolescents as other reasons for the cause.[4] Their research was controversially funded in part by the sugarcane industry through the CDC Foundation; but they deny any conflict of interest.[5] Third, University of Colorado researcher Richard Johnson, found that large amounts of sugar causes tubular damage similar to those in CKDu patients. He argues that the worker’s excessive consumption of sugar is the cause.[6] Each theory has experienced various success in being accepted by the sugarcane companies, but none have been accepted as the outright reason for CKDu. The fourth theory, presented by researchers at Saint Joseph’s University in Philadelphia, will argue that CKDu is caused by a combination of these theories. Our theory is that extreme heat and dehydration combined with toxic agrichemicals weaken the kidneys and leads to CKDu. The reasoning behind this theory will be analyzed in a historical, medical, environmental, and ethical section.

In addition to conflicting theories, treatment availability in Nicaragua adds to the increasing CKDu death toll. Treatment for chronic kidney disease would typically include dialysis or kidney transplant; however Nicaragua is
the second poorest country in the western hemisphere so resources are limited. In 2009, one article reported that less than 10 living donor kidney transplantations were attempted, while in recent years no dead donor kidney transplantations were initiated.[7] Even if the number of transplants were increased, the cost would still be too much for a sugarcane worker, whose monthly income is at most 6,642 (USD 259.6) Cordobas.[8] The estimated cost for kidney transplants in the United States in 2011 was $262,900, which included hospital admission and immunosuppressants.[9] Sugarcane workers rely on the more affordable and accessible treatment, peritoneal dialysis, instead.[10] Peritoneal dialysis requires sanitary conditions, which is difficult to achieve in Nicaragua. Although many precautions are taken such as on-call nurses and “clean rooms,” the realities in their environment can lead to infections and death for the people using at home dialysis programs.[11] In developed countries such as the United States, CKDu is not terminal because treatment is available; however in a country with little resources and inferior sanitation controls, treatment becomes an unattainable luxury.

The CKDu epidemic is a worldwide phenomenon, plaguing other countries besides Nicaragua. Since the mid-1990s, CKDu has killed an estimated 20,000 rice paddy farmers in the North Central Province of Sri Lanka.[12] An additional 400,000 are estimated to be affected by the disease too.[13] In El Salvador, 2,500 deaths from kidney disease occur annually.[14] The difference between Nicaragua and these other countries is how they have combated CKDu. Both El Salvador and Sri Lanka banned glyphosate, as they both acknowledged that it has a direct link to CKDu. El Salvador was the first to ban glyphosate in 2013, while Sri Lanka officially banned the import of glyphosate in June 2015.[15] [16] As for the Nicaraguan agricultural companies, glyphosate is still administered to the sugarcane crops. The Nicaraguan companies defend their use of the chemical by citing the 2012 Boston University study. The report claims that more research would be needed to establish any links between agrichemicals and CKDu.[17] The only action the companies have made is spending $4 million since 2009 on food assistance, health, and housing projects for their employees.[18] Unfortunately, the help does not prevent CKDu. Nicaraguan health policy needs to be changed so that CKDu is prevented instead of treated. Nicaragua needs external and internal pressure to make these changes, which is why this article focuses on this particular country.

Overall, the purpose of this article is to articulate a fourth theory of research that argues a combination of adverse working conditions, environmental factors and the use of glyphosate cause CKDu in Central America. The article will examine this new theory in a fivefold way: first, to examine the historical background surrounding the sugarcane industry; second, to examine the medical issues that have caused the deaths of 20,000 sugarcane workers; third, to examine the environmental issues that are implicated in the cause of CKDu; fourth, to evaluate the ethical issues surrounding CKDu; and fifth, to propose recommendations on how to eliminate CKDu among the sugarcane workers of Nicaragua. With these five points and the new theory, the CKDu topic will be analyzed in a way that calls for change and fights for the rights of the sugarcane workers.

HISTORICAL ANALYSIS

Before the 1990s, CKDu rarely affected anyone, but now the death toll is up to 20,000 people. Something must have changed after the 1990s to cause this epidemic. A historical analysis of the sugarcane industry, Nicaraguan politics, and pesticide usage could suggest a few reasons for such an increase.

Sugar was first introduced to Nicaragua in the 16th century but the product was mainly used in the local markets.[19] In 1982, the first sugar cane factory, Ingenio San Antonio, opened.[20] It is now known as SER San Antonio. The factory is located near Chichigalpa as well as León and Chinandega. Three other sugarcane companies, Monte Rosa, Dolores, and Montelimar opened in 1948, 1960, and 1969 respectively. San Antonio is still the largest company among the four and produces more than 65% of Nicaragua’s sugar, equaling 17,000 metric tons per day.[21] About 9,000 people work at the various factories, mills, and plantations in the San Antonio complex.[22] San Antonio is owned by the Nicaragua Sugar Estates Limited (NSEL), a subsidiary of Grupo Pellas.[23] Carlos Pellas, Nicaragua’s first billionaire, owns Grupo Pellas. Grupo Pellas acquired the plantation in 1980 and has many other businesses related to the sugar industry including the popular Flor de Caña rum.[24] Companies like Grupo Pellas have enabled sugarcane to grow into a multi-million dollar industry for the country. A lucrative industry though could be dangerous as workers’ rights may be jeopardized as a result of obtaining a larger profit.

Raw cane sugar accounts for 5.25% of Nicaragua’s exports which ranks 33rd among main exporters around the
world.[25] It also contributes for 4% to the nation’s GDP.[26] The United States is the biggest buyer of Nicaraguan sugar, importing 33% of the sugar in 2010.[27] Throughout history, the United States seemed to always control how successful the Nicaraguan market was. In the 1930s, when the United States was going through a recession, exports fell.[28] Then in the 1960s when the United States embargoed Cuba in response to the missile crisis, exports tripled for two decades.[29] Finally, during the Sandinista revolutionary regime between 1983 and 1990, Nicaragua suffered from the American embargo made under the Helms-Burton Act.[30] From the 1990s onward, production has risen and the United States continues to import the largest amount of sugar from Nicaragua. These fluctuations in the industry show just how important other countries are to the success of the Nicaraguan sugarcane industry.

Similar to its relations with the United States, Nicaraguan politics have also gone through many changes. With each new political party came new reformations as to how agriculture was produced and distributed. In 1936, Somoza García became President of Nicaragua and created a dictatorship in the country. For the next 40 years, until 1979, the Somoza family controlled much of the land and industries in Nicaragua. In the 1940s, the Somoza government confiscated many agricultural properties like coffee and cattle from German immigrants and sold them to the Somoza family at low prices.[31] With these enterprises that included sugar mills and plantations, Somoza García amassed an estimated USD $60 million by the end of World War II.[32] In 1960, Nicaragua joined the Central American Common Market, which stimulated trade and manufacturing.[34] This establishment in addition to the United States embargo on Cuba, greatly boosted the sugarcane industry, during the Somoza regime.

In 1979, the Sandinista National Liberation Front (FSLN) overthrew the Somoza regime during the Nicaraguan Revolution and introduced new policies that changed the agricultural landscape. The Sandinista economic policies reflected their socialist ideology so major exports were nationalized and the formation of state farms and farming cooperatives was encouraged.[35] They also distributed land to individual peasants and in 1981 drastically weakened the private sector by confiscating businesses that threatened the revolution.[36]

In 1990, the FSLN reign concluded and Violeta Chamorro was elected president of Nicaragua. She changed Nicaraguan policies by privatizing many state-owned industries in an attempt to boost the economy. Privatization improves efficiency within companies because the goal is to cut costs and make a larger profit. Privitization can be dangerous though, because the private monopolies created are not regulated by the government. No regulation could mean worker abuse or illegal actions done for the sole purpose of profit. The privatization of Nicaraguan industries in the 1990s could be why CKDu drastically increased during this time. Sugarcane companies were now unregulated and could have prioritized money over ethics. Since then, the industries have stayed private and profit-driven and coincidentally CKDu rates have continued to grow. Before the 1990s, CKDu was not a major problem; but once the industries became private, CKDu started to appear and has not stopped since.

Many researchers believe that pesticides are the cause of CKDu so a brief look at the history of pesticide usage in Nicaragua could explain why CKDu increased after the 1990s. In the 1950s, pesticide usage began in Nicaragua with the cotton plantations. DDT (dichlorodiphenyltrichloroethane), a colorless, crystalline, tasteless and almost odorless organochloride known for its insecticidal properties, was the primary pesticide used until the 1980s when pesticide poisonings became publicly known.[37] Pesticide usage is problematic though, because it can create more resistant insects and weeds. As a result, more spraying is needed and a cycle forms. Nicaragua fell into this cycle and its pesticide usage was so much that it lead to a public health nightmare. According to a 1972 United Nations Food and Agriculture Organization (FAO) report, 3,000 cases of pesticide poisonings occurred in the year.[39] In the 1980s, coffee, sugarcane, and bananas replaced cotton as the main exports but the amount of pesticide usage remained high. Researchers speculate that out of all pesticides, glyphosate is the most likely to cause CKDu. Although it is unknown when glyphosate was first used in Nicaragua, one could assume that it became heavily used in the era of privatized business due to limited governmental regulations. Glyphosate was introduced commercially in 1974 by Monsanto, so it is possible it was used in Nicaragua before the 1990s; however, in 1996 weeds became resistant to the chemical which prompted more usage.[38][39] This high use of toxic chemicals, specifically glyphosate, could have potentially started the CKDu epidemic. The fact that there were no CKDu cases during the
time of DDT usage supports the theory that the introduction of glyphosate is the reason for CKDu.

The history of sugarcane in Nicaragua is fascinating and important in trying to find out how and why CKDu emerged in the sugarcane industry. The 1990s is a crucial time because it is when CKDu first surfaced. After analyzing the politics and pesticide usage during the time, it can be speculated that the privatized and unregulated companies that started in the 1990s have a link to CKDu. What the companies specifically did during that time is unknown; however it drastically changed the agricultural landscape and its worker’s health. Finally, the use of pesticides in Nicaragua has always been high, but it is possible that certain chemicals were introduced in 1990s that coincidentally caused renal failure. We will argue that glyphosate is the major chemical that is causing CKDu, however without data that shows it actual introduction, this is only speculation.

MEDICAL ANALYSIS

The kidneys are a pair of organs located deep in the posterior aspect of the lumbar regions of the abdomen which function to maintain proper water and electrolyte homeostasis, regulate acid base balance, synthesize hormones, and filter metabolic waste products of the blood while eventually excreting them through urine. Chronic kidney disease (CKD), also called chronic kidney failure or chronic renal failure, is defined as the presence of kidney damage or decreased kidney function for three or more months, irrespective of the cause. Three months of persistent damage or decreased function is necessary to distinguish chronic kidney disease from acute kidney disease.[40] The most common causes of CKD are hypertension, diabetes mellitus, glomerulonephritis, chronic diseases, and repetitive use of nephrotoxic agents such as NSAIDs (i.e. Ibuprofen). Though a serious condition, the early manifestations of CKD may initially go undetected or undiagnosed until kidney function is only about twenty five percent of normal.[41] As kidney damage advances, the body is unable to clear waste products that would normally be removed by healthy kidneys. As a result, waste products accumulate throughout the body causing various metabolic derangements and organ dysfunction. Eventually, if uncontrolled or untreated, the condition reaches a point in which dialysis is required for survival.

PATHOPHYSIOLOGY:

The kidney is broadly divided into a filtering (nephrons) and collecting parts (collecting ducts). Nephrons, the smallest functioning unit of the kidney, are composed of a glomerulus and tubules. The glomerulus functions by filtering plasma into the tubules where water, nutrients, and other necessary electrolytes are absorbed into the blood stream. The remaining waste products reach the collecting ducts from which they are eventually excreted in the urine.[42] In CKD, a decrease in the function of fifty percent of nephrons results in hyper functioning of the remaining nephrons. The compensatory work of the nephrons result in inflammatory changes, fibrosis, and scarring of the glomerulus and tubules of the kidney. A decrease in renal function interferes with the kidneys’ ability to maintain fluid and electrolyte balance. The ability to concentrate urine with electrolytes and waste products declines early and the ability to excrete potassium, acid, urea, creatinine, and phosphate are lost. As the disease progresses, the ability to dilute urine is interrupted causing fluid accumulation throughout the body.[43] The kidney is also unable to produce erythropoietin, the hormone responsible for red blood cell production, and 1-alpha-hydroxylase, the enzyme responsible for Vitamin D activation. Failure to completely activate Vitamin D leads to an imbalance between calcium and phosphorous homeostasis. Platelet dysfunction and lipid accumulation are also common manifestations of advanced renal disease.

SIGNS AND SYMPTOMS:

Patients with a mild to moderate reduction of renal function may not experience any signs or symptoms besides azotemia, an elevation of blood urea and creatinine levels on laboratory testing. Uremia is defined as the clinical manifestations of kidney failure. The earliest manifestations of CKD are fatigue, lethargy, malaise, inattentiveness, weight loss, nausea, anorexia, and loss of libido. As the disease advances the symptoms increase in severity. Potassium accumulation may lead to cardiac arrhythmias and acidosis. An imbalance in calcium and phosphorous homeostasis leads to metabolic bone disease and erythropoietin deficiency results in anemia. Platelet and white blood cell dysfunction due to renal failure result in inappropriate bleeding and an increase in the frequency of infections. Fluid accumulation results in an abnormally high blood pressure and possible heart failure. Ultimately cardiac disease kills the majority of chronic kidney disease patients.
**DIAGNOSIS:**

The diagnosis of CKD is made through routine laboratory testing and imaging. Testing includes urinalysis with examination of the urinary sediment especially for protein and broad, waxy casts. Blood tests include electrolytes, urea nitrogen, creatinine, calcium, phosphate, and complete blood counts. Glomerular filtration rate (GFR) estimates the amount of blood that passes through the glomeruli each minute. The following is used to calculate the GFR using the MDRD (Modification of Diet in Renal Disease) equation:

\[
\text{GFR (mL/min/1.73 m2)} = 175 \times (\text{serum creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American}).[44]
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Based on the GFR, chronic kidney disease is classified into five stages.[45]

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Imaging modalities include an ultrasound of the kidneys which reveal small, fibrotic kidneys.

**MANAGEMENT:**

The general management of CKD consists of controlling signs and symptoms, reducing complications, slowing the progression of disease, and ultimately initiating renal replacement therapy (dialysis) if required. In certain situations, the cause of renal failure may be reversible such as hypovolemia or the administration of nephrotoxic agents. In these cases, correcting the underlying etiology or stopping the nephrotoxic agent is the basis of treatment. However, most often CKD has no cure thus importance goes to preventing the complications of CKD. Low protein diets are recommended to minimize waste products from accumulating in blood. Diuretics are given to relieve swelling and fluid accumulation throughout the body. High blood pressure is controlled with antihypertensives, most commonly angiotensin converting enzyme inhibitors or angiotensin II receptor blockers which preserve renal function. Statins are also given for high cholesterol levels. Vitamin D and calcium supplements are often given to protect bones and lower the risk of developing fractures. In certain situations physicians may prescribe erythropoietin and iron pills which relieve the fatigue and weakness symptoms of anemia. When complete or near complete kidney failure develops dialysis or kidney transplant is required for survival. Dialysis artificially removes waste products and excess fluid from the body by filtering the patient’s blood through a machine.[46] Without these measures life expectancy would be only a few weeks.

**CKDU IN NICARAGUA:**

Sugarcane field workers with chronic kidney disease that we have interviewed in Nicaragua have disclosed that they work for 12 hours a day, in hot and humid weather of up to 40 degrees Celsius, in long pants and long sleeves, with minimal protective gear. They have also described worsening of their disease after using medications prescribed by the company’s physicians. The medical section will discuss the various factors that may cause or aggravate CKDu including dehydration, use of certain medicines, and glyphosate.

Multiple factors related to their working condition can cause acute kidney injury and worsen chronic kidney injury. Excessive exertion by itself can lead to rhabdomyolysis which can easily cause kidney disease. Rhabdomyolysis is a syndrome characterized by muscle necrosis and release of muscle constituents into the blood stream. Excessive exertion causes exhaustion and destruction to myocytes. This occurs because energy supplied to the muscle is insufficient to meet its demand. Insufficient oxygen supply to the cells causes anaerobic metabolism to occur instead of aerobic metabolism. This eventually leads to lactic acidosis, muscle ischemia, and injury/death to myocytes. Myocyte injury leads to release of intracellular muscle constituents which include myoglobin, electrolytes, and creatinine kinase. Myoglobin release causes acute renal failure by promoting intrarenal oxidative stress. It leads to injury to tubular epithelial cells. Myoglobin is also a potent inhibitors of nitric oxide bioactivity, which leads to internal renal vasoconstriction. Vasoconstriction further decreases the supply of oxygen and nutrients to the kidney and leads to kidney ischemia.

Rhabdomyolysis can be aggravated by profound volume contraction. Dehydration and volume contraction diminish the blood flow that is necessary to carry nutrients and oxygen to the muscle. Volume contraction therefore worsens muscular ischemia and rhabdomyolysis.

Rhabdomyolysis can also be aggravated by sweating. Sweating causes potassium loss. Potassium is released from
muscle cells at time of exertion to cause vasodilatation. Vasodilatation increases blood flow and carry of nutrients to muscle cells. Due to the decreased supply of potassium from sweating, vasodilatation cannot occur, and myocytes become more prone to ischemia.

From previous research, Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to be used for patients with chistata, a dysuria syndrome. NSAID is known to cause acute kidney injury. NSAID serves as a cyclooxygenase (COX) enzyme inhibitor. By inhibiting COX, prostaglandin synthesis is also reduced, hence leading to reversible renal ischemia. Prostaglandin acts to preserve renal blood flow and glomerular filtration rate (GFR) by decreasing preglomerular resistance. It vasodilates the afferent arteriole to maintain appropriate GFR. Prostaglandin does not affect renal hemodynamics significantly in healthy people. However, prostaglandin synthesis greatly increases under prolonged renal vasoconstriction. Prostaglandin synthesis is known to elevate in patients with chronic kidney disease, and when there is volume depletion. As a result, NSAID triggered reduction in prostaglandin synthesis leads to decreased blood flow to the kidneys and causes renal ischemia and worsening of chronic kidney disease. Such damage to the kidney can be further aggravated when other renal toxins such as aminoglycoside is used by patients simultaneously.

After talking with various sugarcane workers and their family members in Nicaragua it was clear that gentamycin was shown to be given to sugarcane field workers to treat urinary tract infections. Gentamycin is a type of aminoglycoside, and they are known to cause acute kidney injury as a common complication of therapy. Aminoglycosides is filtered across the glomerulus in its entirety. About 10 percent of the medication is taken up and sequestered in the proximal tubular cells. Very high dosage of the medication can therefore be accumulated intracellularly at the proximal tubule. Acute tubular necrosis occurs as a result.

The sugarcane workers also mentioned the use of fluoroquinolones to treat chistata. Ciprofloxacin, a type of fluoroquinolone, is known to cause crystal induced acute kidney injury. Risk factors for development include impaired kidney function, alkaltotic urine pH, and volume depletion. This type of acute kidney injury is reversible when ciprofloxacin is stopped. Due to this medication’s complication, dose adjustment is required when a patient has a low glomerular filtration rate. Dose adjustment is also required for ofloxacin, and levofloxacin to avoid renal injury. Therefore, plantation workers who are having acute kidney injury secondary to dehydration or rhabdomyolysis may have worsening kidney damage from fluoroquinolone use.

Furosemide was also mentioned as a medication being used for patients who have chistata. Furosemide is a diuretic, and it is commonly used in patients with conditions that leads to edema such as congestive heart failure or cirrhosis. It is also used for hypertension. Inappropriate use of furosemide will lead to decreased tissue perfusion which leads to hypotension, increase in BUN, increase in creatinine, and hyperuricemia. Sugarcane field workers who have either chronic kidney disease or acute kidney injury will require a sufficient amount of intervascular volume to maintain glomerular filtration rate and to avoid renal ischemia. Inappropriate diuretic use in those patients can lead to further kidney damage, which can then change acute kidney injury to a chronic state, or worsen chronic kidney disease.

Finally, glyphosate is a well-known herbicide that is used widely throughout the world. It is used on the sugarcane plantations in Nicaragua as a way to increase the ripening of sugarcane as well as preventing weeds. Glyphosate is the aminophosphonic acid analog of the amino acid glycine. Besides ingestion, glyphosate can enter the body through dermal and respiratory routes. Previous studies have shown low level glyphosate being detected in the urine of farm workers after glyphosate application. Glyphosate can dissolve in sweat and be absorbed transdermally. Farmers tend to work with minimal protective gear, and glyphosate can be breathed in and enter the respiratory tract.

Multiple studies in the past have shown evidence of glyphosate and its effect on the kidneys. Juraunghoorskul et al. have described changes in proximal tubular cells of Tilapia after exposure to glyphosate.[47] Ayoola has illustrated that glyphosate causes development of dilatation of bowman’s space and degenerated tubules in African catfish.[48] Séralini et al. showed that rats fed with glyphosate exposed maize have elevated BUN and creatinine, and reduced kidney weight.[49]

Sugarcane field workers work for long hours and have prolonged exposure to glyphosate in minimal protective gear. Based on previous studies on the effect of glyphosate on renal function, these workers may sustain chronic kidney
injury due to prolonged exposure to glyphosate.

During our visit at Nicaragua, sugarcane field workers with chronic kidney disease described multiple symptomatologies and complications that they suffered. They depicted red/brown urine, white urine, bone and muscle pain, known cardiac disease, known hypertension, and development of fever. Acute kidney injury by itself can cause hematuria. Dehydration along with overexertion can lead to rhabdomyolysis, which causes muscle breakdown and the release of myoglobin into the blood stream. Myoglobin is then filtered through the glomerulus and creates reddish brown colored urine. Sugarcane field workers also complained of white urine. White color in the urine can be caused by chyle, pyuria, or phosphate crystals. Chyle is white urine caused by fat droplet and lymph in the urine. This is seen in a parasitic infection called filariasis. Pyuria and phosphate crystals are seen in urinary tract infections. Previous research has shown the use of antibiotics for those workers to treat urinary tract infections. The sugarcane workers we interviewed disclosed that their medical conditions usually got worse following treatment for the various infections. Presumably, those workers may have a urinary tract infection in combination with kidney failure. As mentioned above, many antibiotics used for a urinary tract infection can aggravate kidney function. As a result, their renal function may have deteriorated while treating for a urinary tract infection.

Sugarcane workers have also described musculoskeletal and bone pain. Those symptoms can be secondary to arthritis from their physically demanding work. CKD, on the other hand, can also lead to musculoskeletal pain. CKD causes diminished production of calcitriol, which is the activated version of vitamin D. It also decreases serum calcium, and increases serum phosphorus. These abnormalities cause increased parathyroid hormone concentration in the blood, which is called secondary hyperparathyroidism. Increased parathyroid hormone consequently leads to bone resorption. Patients with secondary hyperparathyroidism can have musculoskeletal manifestations such as tendon rupture, bone pain, muscle pain, weakness, and periarticular pain.

Besides musculoskeletal manifestations, CKD related bone disorder and mineral metabolism defect also leads to coronary and peripheral vascular calcification, causing coronary artery disease, angina, left ventricular hypertrophy, and congestive heart failure. CKD can lead to anemia of chronic disease, which can further lead to cardiac complications. CKD can also cause hypertension. On the other hand, hypertension can cause CKD.

Fever can occur due to many reasons. Most notably, it occurs from infection. However, fever can occur as a result of physical exertion and working under high temperature exposure as well. Heat stroke, for example, is defined as fever greater than or equal to 105 degrees Fahrenheit with complications involving the central nervous system. It occurs due to prolonged heat exposure and/or prolonged exertion. Sugarcane workers in Nicaragua complain of constant fevers, and it likely occurs secondary to their working condition.

**SUMMARY:**

In summary, sugarcane plantation workers are working under direct sun exposure, high temperatures, for very long hours with minimal breaks. Those working conditions alone can cause severe rhabdomyolysis and acute kidney injury. Prolonged glyphosate use and exposure further damages renal tissue and worsens kidney function. Inappropriate use of antibiotics, NSAID, diuretics can also greatly aggravate kidney damage. Unremitting acute kidney injury eventually transitions to chronic kidney disease. As kidney injury and ischemia continues, chronic kidney disease deteriorates to the point of end stage kidney disease.

**ENVIRONMENTAL ANALYSIS**

The environment may provide two additional reasons for the cause and spread of CKDu. First, increasing climatic changes and rising temperatures increase the risk of dehydration, which has been shown to be a contributor to CKDu. Second, glyphosate can be absorbed into the environment and create health problems for people not working in the fields. These environmental effects have the potential to harm more than just the workers which, is why it is included in this article.

CKDu mysteriously affects certain regions, which creates questions about the disease. Out of all the places that grow sugarcane, only certain geographical areas are affected. Hot, coastal areas like Nicaragua exist as the “hot spots” for CKDu but in similar environments like Cuba, Dominican Republic, and Brazil, CKDu does not occur as frequently.[50] Catharina Wesseling, a physician and epidemiologist from the Institute of Environmental Medicine at Karolinska Institute, admits that the fact is baffling, yet it could have something to do with better working conditions or medical care.[51]
Nicaragua is located close to the Equator at 13.0° N latitude and 85.0° W longitude.[52] The climate is tropical in the coastal and lowland regions with an average temperature around 25 to 27°C (77-80° F).[53] There are two seasons in Nicaragua, the ‘wet’ and ‘dry’ seasons. The wet season is between May and October and the dry season is November to April. The “zafra” or sugarcane harvest occurs during the dry season, when temperatures are at their highest. Since 1960, the annual temperature has increased by 0.9° C as well as the average number of ‘hot’ days per year.[54] Scientists determined that the year 2015 was the hottest year in history, breaking the record set in 2014.[55] If this pattern of increasing temperature continues then the sugarcane workers’ and the global populations’ health will be put in danger. One way to combat this increasing temperature is for countries to follow the Paris Agreement on Climate Change signed in 2016. By following the standards set in the agreement, global temperatures could be reduced by 2°C by the year 2020.[56] It is imperative for everyone’s health that this increasing climate is put to a halt.

Climate certainly increases the risk of dehydration and heatstroke; however, there has been disagreement on whether or not climate actually causes CKDu. In 2013, an El Salvador research team evaluated the geographic relationship of CKDu hospital admission with the proximity to cultivated crops and ambient temperatures.[57] They concluded that high temperatures did not appear to strongly influence occurrence of CKDu, but rather proximity to agriculture where agrichemicals were applied displayed a link.[58] The data showed that areas with higher CKDu hospital admission rates did not correspond with areas of higher mean maximum ambient temperature. They also supported their conclusion with the fact that El Salvador has always been hot, yet CKDu has never been an issue until the 1990s. The report argued that before the 1990s workers were probably dehydrated during work, but because their kidneys were healthy and unexposed to glyphosate, CKDu never came to fruition. They concluded that something must have happened besides an increase in temperature to cause CKDu. The report targeted an increased use of agrichemicals as the change. Our hypothesis is that climate and high temperatures still have a negative effect on the workers although it is not the sole cause of CKDu. We theorize that toxic agrichemicals injure the kidneys and dehydration from hard labor in high temperatures add to the injury, ultimately culminating into CKDu. It is true that many workers were probably dehydrated and never developed CKDu, but as researchers in El Salvador argue, times and policies have changed and the use of chemicals and inferior working conditions may allow dehydration to be more damaging than normal.

In addition to the climate changing, precipitation has changed by decreasing within the last 15 years. In 2014, a severe four month drought hit Nicaragua and affected more than 100,000 farmers.[69] The Global Climate Risk Index of 2014, placed Nicaragua fourth in the countries most affected by extreme weather events.[60] Since 1960, there has been a decrease of 5-6% of average rainfall per decade.[60] Even with a decrease in rainfall, there has been an increase in heavy rainfalls and flash floods. The number of these days has increased by 2.2 per decade since 1960.[61] The changing weather can be very damaging for the agricultural economy and farmers in Nicaragua. Droughts ruin crops and destroy the only source of income for many families. At the same time, heavy rainfall and flash floods destroy unstable or poorly built houses. A shifting environment affects everyone, but with Nicaragua’s proximity to the Equator many of the effects are amplified jeopardizing Nicaraguans all over.

The environmental effects on the sugarcane workers are uncontrollable; however, the chemical use and its effects are controllable. Glyphosate is one of the primary chemicals used in the Nicaraguan sugarcane industry because it ripens sugarcane for earlier harvest. Glyphosate specifically inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), which catalyzes the condensation of shikimic acid and phosphate pyruvate.[62] This prevents the synthesis of three amino acids: tryptophan, phenylalanine, and tyrosine. In preventing the production of these three amino acids, glyphosate causes stress in the sugarcane plant and an earlier ripening. Studies also show that glyphosate increases recoverable sugar and sugar production.[63] Glyphosate is an economical way to produce more sugarcane for less; however, it has the ability to directly and indirectly affect the Nicaraguans associated with the sugarcane industry.

Although glyphosate saves money, it can negatively affect people and its surrounding ecosystem because of its unique chemical properties. For example, glyphosate has been shown to stimulate growth in fungi and increase soil pathogens which can cause citrus variegated chlorosis.[64] CVC is a type of plant disease that negatively affects growth and fruit size.[65] Glyphosate also has the ability to tightly
bind to soil, lowering the tendency for runoff; however if glyphosate does reach water it has a long half-life of more than 35 days.[66] Glyphosate also has little tendency toward hydrolytic decomposition, meaning that microorganisms and sediment absorption are the best ways to decompose it.[67] With glyphosate being such a toxic chemical, it is very dangerous to have it near water sources. When we talked to one local woman from the León region, she described how many individuals who did not work in the fields were also dying from CKDu. The locals believed it was from the well water they were drinking. Although we do not have data to prove this link, it is highly possible that the effects of glyphosate spread further than the sugarcane fields.

The changing climate and the potency of some agrichemicals have greatly altered the Nicaraguan environment. Rising temperatures and decreasing precipitation have increased the risk of dehydration and heatstroke both of which damage the kidneys. Agrichemicals such as glyphosate can change the soil compositions and have the potential to contaminate local water sources, creating many health hazards for all the nearby people. These problems can be avoided, if these chemicals are banned and prevented from contaminating water and countries follow the recommendations of the 2016 Paris Agreement on Climate Change.

ETHICAL ANALYSIS

CKDu is a “silent killer.” The early signs of this disease, jaundice and fatigue, usually go unnoticed, because the sugarcane workers are not well-educated and are desperate to provide for their families financially. Once the disease advances to its later stages CKDu’s treatments, dialysis or kidney transplants, are far too costly for sugarcane workers in Central America. However, the prevalence of CKDu is highest in these sugar producing communities. CKDu has become the leading cause of death among men in Central America. Since 2004, 46% of male deaths in Chichigalpa, Nicaragua—the country with the highest CKDu death rate in Latin America—were caused by CKDu. In the area of Chichigalpa now called “La Isla de Viudas” (the Island of Widows) 7 in 10 men have CKDu. To date, over 20,000 deaths in Central America has been linked to CKDu.[68] The sugarcane industry in Nicaragua has quadrupled in size to a $500 million a year industry, yet at what cost? Young men are dying by the thousands from CKDu and nothing substantive is being done to stop these deaths. One could speculate that profit is driving the industry. Why would the sugarcane industry invest time and money dealing with CKDu when there are many more workers available in Nicaragua to replace the ones that die? Profitability of the sugarcane industry is a priority for the Nicaraguan government and business community. The cause of CKDu needs to be determined now and new procedures need to be put in place to stop the growing death rate from CKDu. This is an imperative because the demand for sugar worldwide is increasing, which will cause an unmonitored expansion of the industry. Ethically, allowing profits from an industry to increase at the expense of the lives of the poor and most vulnerable members of society violates every principle of ethics. It will be argued that—according to the ethical principles of respect for persons, beneficence/nonmaleficence, and justice—action must be taken immediately to address the concerns surrounding the cause of CKDu. Such actions will not only save lives, but will also do much to conquer the mistrust that now exists between the people of Nicaragua and their government and business leaders.

“Respect for persons” refers to the right of a person to exercise self-determination and to be treated with dignity and respect. The principle of respect for persons divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.[69] Numerous abuses of sugar cane workers have been documented in Nicaragua such as: long working days and weeks, inhumane working conditions, inadequate protection from pesticides, unjust salaries, etc. Many of these workers are only hired during the harvest season so they must earn their living for an entire year in just six months’ time.[70] These abuses should be abhorrent to anyone. But for medical personnel who care for these workers in the camps, who should have been trained in human rights and ethical principles, these abuses should have been reported and stopped. To witness or to have known about any of these abuses and not to have reported them or tried to stop them is a direct violation of the principle of respect for persons. Every ethical document from the Hippocratic Oath to the U. N. Universal Declaration of Human Rights clearly state that, “no human person should be subjected to torture or to cruel, inhumane or degrading treatment or punishment.”[71] To highlight the point that these workers are not being treated with dignity and respect, sugar cane companies are under pressure to minimize growing/processing time in order to increase output. The chemicals used to increase output are having serious medical consequences for the sugar cane workers.
needed medical care because of the lack of trust they now have for their physician. A basic tenet of the principle of respect for persons is that one must never use another person as a means to an end. Opponents argue the sugar cane workers are being used as means to an end in an attempt to maximize outputs and achieve the company’s quotas. Human rights and the basic dignity and respect that every person deserves become the casualty.

The failure of company physicians, company executives, and governmental agencies to be proactive in addressing the medical needs of this most vulnerable population in regards to CKDu is causing needless suffering and death. These workers have no choice but to work in the sugar cane fields because it is the only work available to them. It is a matter of survival. The cause of CKDu must be determined now and new policies must be initiated to protect this vulnerable population. To deny the sugar cane workers safe working conditions and proper medical care clearly violates the ethical principle of respect for persons.

The principle of beneficence involves the obligation to prevent, remove, or minimize harm and risk to others and to promote and enhance their good. Beneficence includes nonmaleficence, which prohibits the infliction of harm, injury, or death upon others. In medical ethics this principle has been closely associated with the maxim primum non nocere (“Above all, do no harm”). Sugar cane workers and the people of Nicaragua have the right to know what is causing the death of 20,000 men and women who work in the sugar cane fields. This enigmatic kidney disease is a silent killer affecting agricultural workers and others in Central America. Family members and sugar cane workers argue that the government of Nicaragua is corrupt and in collusion with private industry to promote profit. The government argues that it is doing everything possible to promote and enhance the good of the sugar cane workers. The problem is that this is a contradiction because the cause of CKDu still remains a mystery.

Researchers are investigating the various causes for CKDu but the epidemic continues. Clearly there is a link between heat stress, dehydration, working conditions and pesticides. The sugar cane industry and the Nicaraguan government argue that they have instituted new policies to keep the workers safe and alive. Industry executives stipulate that there are mobile clinics equipped with a cooling area that takes blood and urine samples and offers hydrating beverages and food for workers in the fields. They also claim that they pay workers for a seventh day of rest.
Opponents argue that there are not enough medical supplies and hydration packets for the number of workers in the fields. They also argue that the mobile clinics only screen workers that are not sick, and then whenever there are visitors to the fields, more provisions are provided.[vi] Even if the intentions of the government and sugar cane industry are good, the unjust working conditions and use of pesticides in the fields is a violation of nonmaleficence.

There is clear evidence from studies over the past 50 years that there has been a negative impact of pesticide use in Nicaragua. There has been underreporting of acute pesticide health effects, but since the 1980s this evidence has become clear. Studies have concluded that pesticide use in Nicaragua is causing acute and chronic effects and that there is a high acute pesticide poisoning incidence rate in the general population.[73] Glyphosate is causing direct harm to the sugar cane workers. Glyphosate attacks the kidney tubule. It binds to the heavy metals, and that compound lasts in the body for a very long time—with over a 20-year half-life—thus the first word in the epidemic disease chronic kidney failure. Since glyphosate can be inhaled, ingested, or absorbed through the skin, farmers and sugar cane workers are especially at risk of being exposed. Furthermore, the human liver, which is normally responsible for eliminating heavy metals and other toxins from the body, cannot detect glyphosate, so it bypasses this important purification step, and goes straight into the kidney tubules. The glyphosate and heavy metals then attack the kidneys, causing severe disease.[74] In addition, due to the poor working conditions and frequent dehydration of the workers, company physicians and pharmacists in Nicaragua are prescribing medications such as diuretics, antibiotics and NSAIDS for symptoms that may be related to dehydration and volume depletion. These factors, alone or in combination, may be possible contributors to kidney damage. Researchers are highly recommending that acute kidney damage coupled with volume depletion and exposures including medications and infectious agents should be further evaluated as causal factors for CKDu in Nicaragua.[75] There is a need to do what is in the best interest of these sugar cane workers. Twenty thousand innocent lives have been lost and more will die unless we maximize benefits and minimize harms—ban the use of glyphosate and other pesticides. This can only be done by funding further research in this area, instituting government regulations on working conditions, and banning glyphosate use in the sugar cane fields. Failure to recognize this great need is a failure not only of the test of beneficence; it may also be a failure of the test of nonmaleficence.

The principle of justice recognizes that each person should be treated fairly and equitably, and be given his or her due. The principle of justice can be applied to the circumstances of “dual loyalty” when sugar company physicians must choose between responsibility for their patients in need of medical care and the demands placed upon them by executives of the sugar cane industry. The most common rationale for medical professionals’ willingness to participate in or overlook the various incidents of abuse is their sense of duty to their employer. When company physicians are called upon to treat sugar cane workers for symptoms of CKDu many believe they are acting in the best interests of the workers, the nation and humanity. The argument is that the medical professionals have a moral duty to ensure that medical care for the workers is carried out in the most fair and humane way possible. They argue that they are treating these workers with the best medications available. Opponents argue that these physicians violate the basic tenets of human rights law and the ethical standards of the medical profession. It may be true that the physician’s participation is offering some degree of humanness to the situation because they are seeing and treating these workers. However, they are ignoring symptoms at times, sending workers back into the fields to further damage their kidneys, knowing full well, none of these workers if they have CKDu could ever afford dialysis. Is this treating someone fairly and equitably? These physicians must know that CKDu is an epidemic. They must know the symptoms of CKDu. They must know that the working conditions are unjust and harmful to the workers. They must know or at least suspect that glyphosate is a major issue regarding CKDu. Finally, they must suspect that the medications they are prescribing will not help these workers in the long-run. Every medical professional has the right, with a well-formed conscience, to refuse any order that he/she believes is unjustified and personally unethical. Every medical professional has the duty to report conditions he/she believes could be the cause of this mysterious epidemic. The failure of medical professionals to recognize that their duty as an employee of a particular company can never trump medical ethical principles is clearly an injustice. It is an injustice not only to those who were abused but to humanity as a whole. If the principle of justice mandates that each person should be treated fairly and equitably, then the participation of medical professionals in cruel, inhumane and
deteriorating treatment of workers clearly violates the principle of justice.

We Americans espouse the belief that all men and women are created equal. Equality has also been a basic principle of the medical profession. If we truly believe in equality, we should insist that all men, women and children receive equal medical treatment and resources. Denying knowledge of medical treatment to individuals suffering from CKDu, treating such workers and then sending them back into the fields where they will be further compromised without due warning, violates a basic tenet of justice. Physicians and clinical researchers have an ethical obligation to draw attention to this mysterious disease. However, as a matter of justice, it is not only these professionals who have an ethical obligation to inform the world about this epidemic. It is the responsibility of all wealthy nations and international developmental agencies to solve this medical mystery. Not because it is solely in the best interest of the sugar cane workers in Nicaragua, but because Central America exports a large amount of raw sugar to developed nations. The raw sugar, because of pesticide use, could have adverse effects on others as well. Failure to find the causes of CKDu is ethically irresponsible and morally objectionable. To compromise the basic ethical foundations upon which medicine stands is destructive not just for the sugar cane workers of Nicaragua but for humanity as a whole.

To address these medical, environmental and ethical concerns, we propose various recommendations to address CKDu now and in the future. Unless the world community addresses these needs for additional education and proposes new policies we will never attain the goal of eradication of CKDu. We hope our recommendations will not only save valuable medical resources; but have the potential to save precious human lives. If we do not make this a priority now, everyone will pay a price in the future.

RECOMMENDATIONS

1. The United Nations should ban glyphosate in Central America and in the world as a pesticide. The potential links between glyphosate and CKDu are enough to prove the toxicity of the chemical. Continuing to use it at the industrial and commercial level is endangering too many people. The glyphosate ban should follow the models set by El Salvador and Sri Lanka when they banned the chemical in 2013 and 2015, respectively. Removing the chemical has not economically affected the sugarcane industry as proof of El Salvador’s similar production before and after the removal.[78] By banning glyphosate, a potentially deadly risk is being eliminated.

2. Safer workplaces should be provided through the implementation of hydration, rest and shade policies, hydration backpacks like CamelBak®, shortened working hours, and proper medical care. Workers should also be given access to better pesticide training and effective protective gear before each harvest and an age requirement should be established for handling pesticides. An example of an effective policy would be the policies initiated by El Salvador that ensure worker safety. At the sugar cane mill Ingenio El Angel, at least 65 workers were given rest, water, and shade throughout the harvest. As a result, since the start of the program, kidney functions have stabilized and heatstroke has been eliminated.[79] If these programs were to be brought to Nicaragua along with an effort to reduce pesticide poisonings, then the number of CKDu patients and deaths could decrease.

3. Sugarcane fields must be a minimum of 300 meters away from any houses. While talking to sugarcane workers and their family members, we learned that some people not working in the fields also developed CKDu. If the houses are close enough to the field then pesticide spray could be carried by the wind and breathed in by the families not working in the field. There is also a risk of chemicals entering the local water supply via runoff or spills. By moving houses further away from the sugarcane fields, then the risk of non-workers developing CKDu is eliminated.

4. The World Health Organization and other international medical organizations should provide additional funding for research on glyphosate and CKDu immediately. The research regarding glyphosate and CKDu is still new and heavily disputed. Until a theory is universally accepted, then sugarcane companies will continue to dispute the facts and remain unchanged. Research about the effects of glyphosate and dehydration together could be very instrumental in changing the policy for pesticide usage.

5. Nicaragua should institute new government regulations for sugar cane workers in line with international standards. The International Labour Organization (ILO) has many guidelines in place for worker’s rights. One example is a limit of eight hours a day and forty-eight hours in a week for a worker in the industrial business.[80] Another example is for the employer to provide maximum safety to their employees at work which includes preventative safety, promotion of relevant instruments and tools for the job, and technical assistance while working.[81] Following these regulations would ensure worker safety.

6. Health care workers, ethicists, human rights advocates, etc. must begin to raise national and international awareness about CKDu issues. The CKDu epidemic has gained a lot of attention in recent years; however, more awareness is needed. With more awareness in the international market, more pressure will be put on the Nicaraguan sugarcane companies and the Nicaraguan government to make beneficial changes for their employees and citizens.
7. The Nicaraguan government must provide water filtration systems for the affected areas. As stated above, the families that we spoke to in Nicaragua explained how non-workers who lived near the sugarcane fields still developed CKDu. One of the possible causes is water contamination from pesticide usage on the sugarcane. Water testing and water filtration systems would provide safe drinking water for the workers and their families.

8. The Nicaraguan government must immediately enact the 2016 Paris Agreement on Climate Change recommendations to lower the world temperatures. Climate change has seriously affected the sugarcane workers in Nicaragua. The higher temperatures increase the worker’s risk of getting heatstroke and dehydration. The goal of the Paris Agreement is to reduce global average temperature to well below 2°C by the year 2050. [82] If the Paris Agreement is followed and temperatures are decreased then the sugarcane fields will be cooler and the workers’ health could improve.

9. The Nicaraguan Ministry of Health must provide better education for physicians and other health care workers on the effects of dehydration and pesticides on a worker’s kidneys and liver. A physician’s job is to treat and ensure the health of his/her patients. In some cases, the sugarcane workers are either misdiagnosed or given an incorrect treatment for their disease. These incorrect treatments can worsen the effects of CKDu as discussed in the medical analysis section of this paper. If physicians were specially trained to treat patients with CKDu, then many workers would receive the proper care. Training could include an overview of what medications are allowed for CKDu patients as well as ways to avoid further injury to the kidneys. Many of these workers have limited knowledge about CKDu and how to protect themselves from injury. Physicians have the professional and ethical responsibility to help them understand their disease and to better their health. This can be done with additional training and education for the physicians.

CONCLUSION

The CKDu epidemic in Nicaragua is a medical, environmental, and ethical problem that has gone on for too long. Too many workers have succumbed to the disease and still no action has been initiated to fix it. The causes have been debated, but through observations and a comprehensive literature review it has been determined that the increasing temperatures, terrible working conditions, and the use of agrichemicals as such glyphosate are all reasons for CKDu. CKDu is not solely a medical problem, it is an environmental and ethical dilemma as well. The chemical glyphosate is terrorizing the workers and depleting the ecosystem where it is used. The rising climate is increasing dehydration rates and burdening the agricultural industry. Ethically, something has to be done to save the lives of these workers, but profit takes priority for these companies. With pressure from world leaders, international organizations and human rights groups, changes can come about in the fields of Nicaragua and the voices of these dying men and woman can finally be heard.

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