

Is Glyphosate a Key Factor in Mesoamerican Nephropathy?

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Abstract

Mesoamerican nephropathy (MeN), also known as chronic kidney disease of unknown etiology (CKDu), is an unusual form of kidney disease not associated with diabetes, hypertension, or glomerular nephritis. It has a number of known risk factors, none of which adequately explain the skyrocketing prevalence of the disease among sugarcane workers in El Salvador and Nicaragua. In this paper, we narrow the research focus from agricultural chemicals, in general, to glyphosate, in particular, an herbicide routinely used on sugarcane. We explain how glyphosate compellingly contributes to CKDu, by reviewing the evidence for glyphosate's direct toxicity to kidneys and showing how the herbicide amplifies the damage to kidneys from other known risk factors. Using standard web search on index words and phrases, we gathered and perused a large collection of papers describing the pathology of MeN and associated metrics, on the one hand, and the mechanisms of toxicity of glyphosate in humans, animals and *in vitro* studies, on the other hand. We show that glyphosate is used on sugarcane in three distinct ways, with exposure greatest when the herbicide is used as a ripener near harvest time. We identify several pathologies associated with MeN that have been found to be implicated in papers on glyphosate exposure, such as enhancing the growth of Clostridia species and fungus, promoting arsenic toxicity, suppressing the synthesis of adrenocorticotropic hormone (ACTH), disrupting fructose metabolism, and promoting dehydration and high serum urate. A companion paper explains how glyphosate's substitution for glycine could cause additional renal damage. Together, these two papers strongly suggest that glyphosate is a causative agent in CKDu. Overall, the research literature provides compelling evidence that glyphosate exposure is a significant factor in MeN. Glyphosate usage on crops should be curtailed in order to protect the agricultural worker population from this devastating and life-threatening disease.

Keywords: Chronic Kidney Disease of unknown etiology (CKDu); Mesoamerican Nephropathy (MeN); Glyphosate; Sugarcane; Nicaragua; El Salvador

Introduction

Mesoamerican nephropathy (MeN), also known as chronic kidney disease of unknown etiology (CKDu), is an unusual form of kidney disease specifically not associated with diabetes, hypertension, or glomerular nephritis. The unique symptomatic profile of MeN includes asymptomatic reduction in glomerular filtration rate, hyperuricemia, hypokalemia, tubulointerstitial disease with secondary glomerulosclerosis and glomerular ischemia. Unlike most types of kidney disease, blood pressure is not elevated, and, in fact, hypotension could be considered a feature of the disease. Hyperosmolarity due to extreme dehydration activates the vasopressin and aldose reductase-fructokinase pathways that can lead to renal injury [1]. MeN's prevalence has exploded among young male agricultural workers in Nicaragua and El Salvador in the past decade, with sugarcane workers being the most acutely affected. Figure 1 shows CKD mortality rates in various countries in North America, revealing the striking anomaly for males in Nicaragua and El Salvador. Figure 2 shows mortality as a function of age, again showing that men 25-59 years old from El Salvador and Nicaragua are especially susceptible to CKD mortality, compared to women and to other countries in North America.

Between 2005 and 2012, there was a 50% increase in hospitalizations for CKD in El Salvador, making it the leading cause of death in adults in the country's hospitals [2,3]. The disease is more prevalent in the Pacific lowlands of these countries compared to communities at higher elevations (18% vs 1%) [4]. While sugarcane workers are the most affected among the agricultural communities, a study by Peraza et al. found that those sugarcane workers who work along the Pacific coast were ten times more likely to have elevated serum creatinine (a marker for kidney disease) than highland workers ($p < 0.001$) [5]. The unique symptom profile of CKDu challenges the mind to explain the underlying

etiology. It seems likely that intense physical labor in tropical heat might lead to dehydration that stresses the kidneys. It has also been suggested that nonsteroidal anti-inflammatory drugs (NSAIDs), used to ease pain, might work synergistically with dehydration to compromise kidney function. Other contributing factors may include exposure to pesticides and toxic metals, such as arsenic, cadmium, aluminum, iron, and lead [6,7]. Mycotoxins such as ochratoxin and aflatoxin have also been linked to the disease [8]. But these factors seem inadequate to account for the extreme devastation of the disease process.

A study by VanDervort et al. published in 2014 specifically addressed the question of whether high temperature or agricultural chemicals were the most significant factors in CKDu. They wrote: "High temperatures do not appear to strongly influence occurrence of unCKDu proxies. CKDu in El Salvador may arise from proximity to agriculture to which agrochemicals are applied, especially in sugarcane cultivation" [9]. A paper by Clark et al. published in 2016 proposed that the CKD associated with sugarcane agriculture in Nicaragua is likely due to a combination of glyphosate toxicity and dehydration due to heavy labor in extreme heat [10].

A 2014 study on farming communities in El Salvador found that 96% of the study subjects had contact with agrochemicals [11]. 89%

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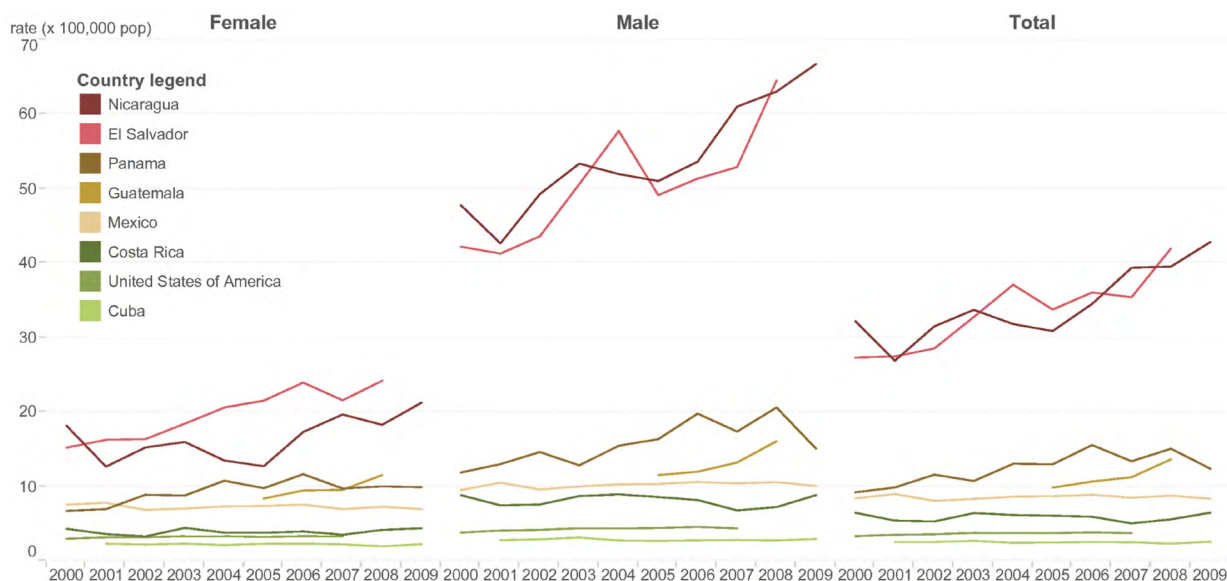


Figure 1: Chronic kidney disease (N18; International Classification of Diseases, tenth revision [ICD-10]) age-standardized mortality rate, selected countries, 2000–2009. Reproduced from Ordunez et al. [2].

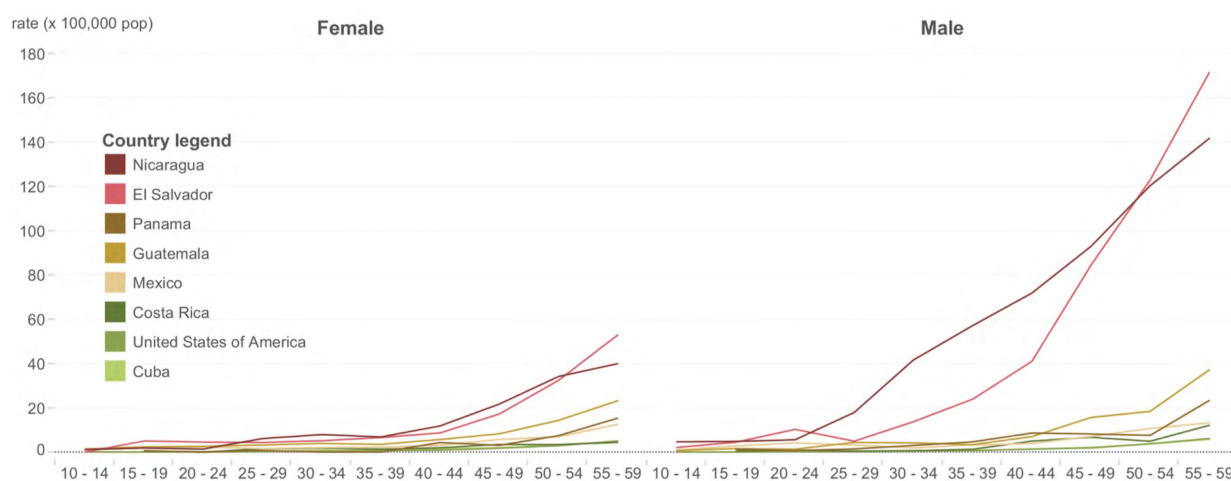


Figure 2: Chronic kidney disease (N18, ICD-10) age-specific mortality rate, selected countries, around 2008. Reproduced from Ordunez et al. [2].

of the study participants were farmers, and 76% experienced profuse sweating. Diabetes was present in only 4% of the patients. They proposed that “nephrotoxic environmental agents” play a key role in the disease process. In fact, another paper from the same issue was aptly titled, “Chronic Kidney Disease of Unknown Etiology Should Be Renamed Chronic Agrochemical Nephropathy” to draw more attention to this aspect of the disease process [12].

Glyphosate is the most common chemical used to induce the maturation or ripening of cane in order to increase the sugar content at harvest time [13,14]. It is also used to kill weeds and is the most widely used herbicide for the eradication of cane stools in preparation for new planting [15]. Glyphosate is not the only herbicide used on cane, but its fingerprints on CKDu demand a special focus. A series of papers by Jayasumana et al. linked glyphosate exposure to a nephrotic disease among rice growers in Sri Lanka that is similar to MeN [6,16,17].

Urinary excretion of heavy metals and glyphosate were found to be markedly elevated in people living in areas where Sri Lankan agricultural nephropathy was endemic. It is significant that MeN first appeared in the mid 1990’s, just as agricultural usage of glyphosate was ramping up. During the period when hospitalizations for CKD in El Salvador increased by 50%, the global use of glyphosate for agricultural purposes nearly doubled, increasing from 388,729 metric tons to 716,676 metric tons [18]. Over the last decade, 6,078,138 metric tons of glyphosate have been applied [18]. In 2008, the Monsanto Company, whose Roundup herbicides are the largest global brand, signaled its interest in increasing cane’s tolerance to glyphosate with the purchase of the world’s largest sugarcane breeding company, CanaVialis.

Dietary Factors

A significant marker of MeN is hyperuricaemia, and diet plays an

important role in influencing urate synthesis by the liver. In particular, both alcohol and fructose are known to increase hepatic urate synthesis, and breakdown of purine-rich foods yields urate as a by-product [19]. Urate can be toxic to the kidney when it precipitates out, forming crystals. It is clear that agricultural workers along the coast in Mesoamerica have an increased risk to MeN compared to those working more inland and at higher elevations [5]. While this difference has been attributed to the higher temperature at sea level, another likely synergistic contributor could be increased access to dietary seafood in a coastal region. Seafood has high levels of purines, which, through their breakdown, can contribute to high urate levels. Seafood is also a good source of heme iron, and iron overload, particularly in the context of glyphosate, can damage the kidneys. Finally, seafood can be contaminated with toxic metals, especially arsenic [20]. A US-based study on a National Health Nutrition and Examination Survey (NHANES) population from 2003 to 2006 found higher levels of urinary arsenic, in both organic and non-organic forms, for those who consumed seafood on a regular basis [21].

“Lija” is a homemade alcoholic drink that is popular in Nicaragua. Consumption of lija is associated with a more than 2-fold increased risk to MeN [22]. Lija is sometimes stored in industrial metal containers that previously held pesticides. It has also been suggested that heavy metals such as lead may have leached into the beverage from processing and storage containers. Glyphosate was first patented as a chelating agent [23]. As such, it would be effective in leaching metals such as aluminum and lead from containers. Fructose from sweetened beverages, popular among day laborers in Central America for quenching thirst, is another likely contributor to elevated urate [24-27]. A human study on obese subjects showed a remarkable differential between glucose and fructose in terms of their effects on serum urate [24]. Consumption of fructose as 25% of energy requirements for just 10 weeks, compared to glucose, induces a highly significant increase in circulating uric acid ($p < 0.0001$). The mechanism by which fructose effected this increase is thought to be due to depletion of ATP and inorganic phosphate, due to increases in

fructose-1-phosphate and glyceraldehyde-3-phosphate synthesis from fructose. This leads to increased nucleotide degradation into uric acid [28]. Fructose may also lead to upregulation of de novo synthesis of purines from glycine [29].

A study comparing fructose-fed Sprague-Dawley rats with dextrose-fed rats revealed that fructose had a direct toxic effect on the kidneys [30]. Fructose-fed rats had greater protein excretion, higher serum creatinine, more renal hypertrophy, and higher mortality. Histologically their kidneys showed more glomerulosclerosis, tubular dilation, tubular atrophy, interstitial inflammation and interstitial collagen accumulation. The renal tissue showed higher levels of the inflammatory cytokine monocyte chemoattractant protein-1 (MCP-1). Dehydration activated the aldose reductase pathway in mouse kidney, leading to an increase in renal sorbitol and fructose levels [31]. This was associated with renal injury, indicated by an increase in serum creatinine and renal MCP-1, proximal tubular cellular injury, and renal fibrosis. It was proposed that this could be a model for MeN, and that high-fructose drinks could exacerbate the damaging effects of endogenously generated fructose in human kidneys.

Smoke Exposure from Burning Cane

The most at-risk group for MeN appears to be sugarcane workers, and increased symptom manifestation is linked to the harvest season, when strenuous labor is involved with cutting the sugar cane stalks with a machete and workers are exposed to smoke from burning cane [32-36]. Similar to other cane-growing countries, cane fields in Nicaragua and El Salvador are burned as close to harvest time as possible to reduce leafy material and facilitate transportation and processing. The burning of the sugarcane stalks previously exposed to glyphosate at harvest time is likely a source of toxic glyphosate-containing fumes, further contributing to exposure risk. A study from 2014 showed that burnt sugarcane harvesting caused an increase in serum creatinine

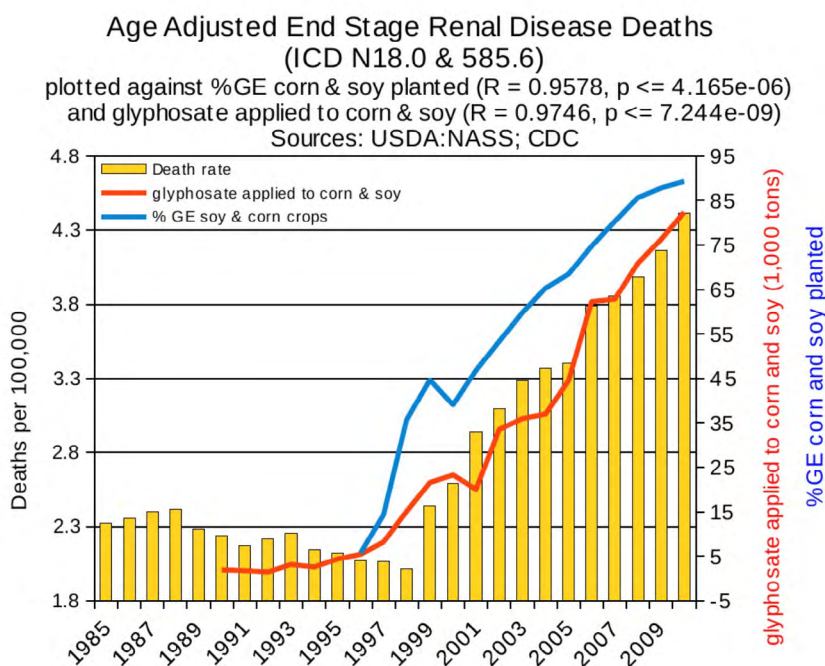


Figure 3: Correlation between age-adjusted End Stage Renal Disease deaths and glyphosate applications and percentage of US corn and soy crops that are genetically engineered. Reproduced from Swanson et al. [80].

and decrease in glomerular filtration rate, along with rhabdomyolysis, hypovolemia, systemic inflammation and oxidative stress [32]. A highly significant increase in micronucleus formation in oral epithelial cells and lymphocytes during the sugarcane harvest season ($p < 0.001$) suggests genotoxicity of chemicals released into the smoke [33]. Jiaqiang et al. show the ability of amino acid transporters to transfer glyphosate from the nose to the brain then directly into the central nervous system [37]. This bypass of the liver could delay metabolism of the molecule. Dermal exposure could do the same [38].

Uremic Toxins

One of the key factors in glyphosate toxicity is its ability to act as an antibiotic, preferentially killing beneficial species in the gut and encouraging pathogens to overgrow [36,39,40]. Clostridia species are especially resistant to glyphosate, and they produce multiple uremic toxins such as p-cresol sulfate and indoxyl sulfate [39]. In fact, chronic CKD is a strong risk factor for *C. difficile* infection [40]. p-Cresol metabolites accumulate during CKD, and there is a shift from sulfation to glucuronidation upon progression, suggesting sulfate depletion [41-43]. Furthermore, proximal tubular epithelial cells transition to mesenchymal cells (EMT) upon exposure to p-cresol sulfate, leading to fibrosis. Several fungus communities, including *Aspergillus*, colonize sugarcane fields [44-46]. The *Aspergillus* species produce a large number of mycotoxins that are nephrotoxic, such as aflatoxin B1 (AFB1), ochratoxin A (OTA), and fumonisins [47-51]. Two examples of nephrotoxic mycotoxins will be discussed here: AFB1 and OTA. The United Nations' Food and Agricultural Organization estimates that 25% of all food is contaminated with mycotoxins [52]. Food and fields should be considered as exposure pathways since both AFB1 and OTA can permeate through the skin [53]. Takahashi et al. found *Aspergillus flavus* and *Aspergillus parasiticus*, which produce AFB1, in 53% of cane field soils sampled and aflatoxin in 89% of sugarcane stems [52]. Thirty-one patients with CKDu in Sri Lanka showed aflatoxins in 61.29% and ochratoxins in 93.5% of urine samples [54]. In Tunisia, OTA was detected in the blood of the majority of people with CKDu [55].

Sugarcane can be harvested by machines or cut by hand. Though mechanical harvesting can be less expensive than manual labor on large plantations, cutting by hand with machetes remains common in Mesoamerica [56-58]. Cane cutters cut at the base of the stalk, where the most sucrose is located. This also is the main location of fungal growth [45]. It is not uncommon for cane workers to chew on raw cane, another possible exposure pathway for mycotoxins.

Several studies demonstrate that glyphosate impairs agricultural soil ecosystems [57-60]. Even though fungi, bacteria, and plants all have the shikimate pathway, glyphosate influences individual organisms in different ways [61]. For instance, aflatoxins adapt not only to the very high temperatures found on the Pacific coastal plains in Central America, where sugarcane is grown, but also to glyphosate [44]. Barberis et al. reported, "All strains of *Aspergillus* section *Flavi* assayed were tolerant to glyphosate." The use of glyphosate on sugarcane fields creates conditions favorable to *Aspergillus* and their toxic secondary metabolites by inhibiting the growth of mycorrhizal fungi and stimulating the growth of phytopathogenic fungi [62,63]. These fungi use glyphosate as a nutrient and an energetic substrate [58,64]. The use of glyphosate was associated with an uptick in cereal diseases from *Fusarium* pathogens in Canada [65].

Bennett and Klich in their comprehensive review of mycotoxins state that, "in the absence of appropriate investigative criteria and reliable laboratory tests, the mycotoxicoses will remain diagnostically

daunting diseases [48]. Still, much is known about specific renal assaults by mycotoxins. OTA accumulates in the proximal tubule and causes oxidative stress and tubular damage [50,66]. It also inhibits ATP mitochondrial production [48]. Aflatoxins are carcinogenic, mutagenic, toxic to the liver and kidneys and immune suppressants, and they inhibit several metabolic systems [48,67,68]. AFB1 induces tubular damage and glomerular injury [69]. In animal studies, it also provokes oxidative stress in renal tissue [66,70,71]. Cytochrome P450 (CYP) enzymes help metabolize and clear most drugs and other xenobiotics. In the kidney, they reside predominately in the proximal tubules [72,73]. They are located there to deal with proximal tubular toxicants like NSAIDs and OTA. Glyphosate inhibits the CYPs [39]. The combination of the degradation of tubular integrity and the compromise of CYPs could boost the damage from a chemical insult, fungal toxicity, or physiological stress.

Glyphosate and Hepatic/Renal Damage

In this section, we review the research literature linking glyphosate to hepatic and renal damage, based on human epidemiological studies, animal-based studies, and *in vitro* studies. A cross-sectional interview study was conducted in 2011 in communities of the Bajo Lempa region of El Salvador, involving 42 males with confirmed MeN [2,3]. All of the subjects reported buying and managing pesticides, and 73.8% specifically reported occupational exposure to glyphosate. The mechanism by which glyphosate achieves an increase in sugar to starch ratio involves inhibition of phosphoenol pyruvate carboxylase (PEPC) [74]. Glyphosate's inhibition of EPSP synthase, which also has PEP as substrate, within the shikimate pathway, is believed to be the main mechanism of glyphosate toxicity to plants [75]. As PEP accumulates due to suppression of the enzymes that metabolize it, it suppresses its own synthesis from fructose, leading to an increase in sugar content in the crop.

It can be anticipated that a similar pathology would occur in the gut of a human consuming fructose, because gut microbes also use EPSP synthase in the shikimate pathway to produce aromatic amino acids with PEP as substrate. Excess fructose consumption is believed to be a significant factor in fatty liver disease, because the liver converts fructose to fatty acids in order to prevent it from reaching the general circulation [76]. Fructose is ten times as potent as a glycyating agent as glucose, and therefore it is essential for the liver to clear it from the circulation. Metabolomic and proteomic analysis showed activation of biomarkers linked to non-alcoholic fatty liver disease and subsequent steatohepatitis in response to ultra-low doses of glyphosate-based herbicides [77]. Ultrasound examination indicated fatty liver disease in 93.5% of patients in El Salvador suffering from MeN [11]. Excess fructose exposure in the liver will also increase the hepatic production of urate. An epidemiological study by Swanson et al. examined correlations between the rise in incidence of a large number of debilitating diseases and glyphosate usage on core crops in the United States [78]. In particular, Figure 1 in this paper (reproduced here as Figure 3) shows a striking correlation between deaths due to end stage renal disease and glyphosate usage between 1997 and 2010. The correlation coefficient was 0.975 with a p -value of $7.24E-9$.

A study based in China involved 80 cases of poisoning by glyphosate through intentional ingestion of Roundup [79]. Multiple organs were affected, but especially the gastrointestinal tract. Fourteen percent of the 80 cases experienced renal damage. A characteristic symptom preceding death (which occurred for 7 patients) was severe hypotension unresponsive to either intravenous fluids or antihypotensive agents

(vasopressor drugs). As we argue in a companion paper, we believe that glyphosate can disrupt the function of aquaporin, which is normally upregulated in the renal tubules in response to vasopressin and protects from renal water loss through urine. In a study of 245 patients in a Korean population, 26% of patients exposed to toxic levels of glyphosate developed hypotension, and this was associated with elevated levels of creatinine as well as long QTc interval [80]. Hypokalemia, a key feature of MeN, is one of the most important risk factors for QT prolongation [81]. Long QT syndrome is associated with kidney disease [82,83]. In a study of patients with chronic renal failure, 41% suffered from QT prolongation, and this was correlated with the number of years of kidney failure and with low serum potassium and calcium levels [82].

A study on rats involving a low-dose exposure to Roundup and/or GM Roundup-Ready feed over the entire lifespan revealed damage to the liver and kidneys, increased risk to various tumors, and early death in the treatment groups [84]. The authors noted that 76% of the discriminant variables versus controls were kidney-related. A subchronic toxicity study on rats exposed to 375 mg/kg glyphosate for eight weeks showed damage to the stomach, pancreatic acinar cells, spleen, brain, liver and kidney [85]. Through histopathological examination of the kidneys, the authors noted glomerular degeneration, mononuclear cell infiltration into the interstices of the tubules, and tubular necrosis. Prior supplementation with zinc ameliorated these effects. Serum urea is an indicator of an excessive breakdown of proteins and/or insufficient clearance due to kidney disease. A linear relationship between serum urea levels and urinary glyphosate was found in a study on dairy cows exposed to high levels of glyphosate in their GMO feed [86]. A study comparing patients with CKD with controls revealed a highly significant doubling on average of the serum urea levels ($p < 0.001$) [87]. Glyphosate increases the production of reactive oxygen species, resulting in oxidative stress, especially in the liver, kidneys and testis [77,88,89]. Consistent with this, a comet assay study revealed DNA damage in subjects from Ecuador exposed to glyphosate, suggesting a genotoxic effect of glyphosate [90]. An *in vivo* transcriptome investigation involving female rats exposed to ultra-low doses of Roundup (50 ng/L glyphosate equivalent) demonstrated an increased incidence of liver and kidney pathologies [91]. A chronic glyphosate-exposure study on 198 male mice carried out by Bio/dynamics in 1983 and submitted to Monsanto found four cases of renal tubule adenomas, an extremely rare kidney tumor, among the exposed mice [92]. The probability of observing this rare tumor four times in 198 mice is $p = 0.0064$, when considering the historical controls of the same laboratory.

Urate

A paper from 2015 argued that MeN might be a uric acid disorder [31]. Male workers exposed to heat stress along with physical exertion are predisposed to recurrent water and volume depletion, often accompanied by urinary concentration and acidification. Uric acid is generated during heat stress, in part because of nucleotide release from damaged muscles. Crystal formation in the kidneys is then the source of renal damage. These authors confirmed that urate crystals were commonly found in the urine of sugarcane workers in El Salvador. Elevated serum uric acid was a consistent metric for MeN in a study based in El Salvador [34]. A recent study on patients with MeN in northwestern Nicaragua compared their disease metrics with those associated with members of the NHANES database suffering from CKD. Multivariable regression analysis revealed that serum uric acid levels were on average 2 mg/dL higher in patients with MeN compared with their NHANES counterparts [87].

Hyperuricemia is directly associated with progressive kidney

failure [93-95]. Hyperuricemia is also an independent risk factor for later development of CKD [96-99]. Acute uric acid nephropathy occurs following renal tubular obstruction by uric acid crystals. As the pH becomes more acidic during the course of concentration of urine in the tubular system, the concentration of urate needed for precipitation of crystals goes down. In animal models of uric acid nephropathy, precipitation of uric acid crystals obstructs the tubules, collecting ducts, pelvis and ureters. Crystal deposition increases tubular and intrarenal pressure, and compression of the renal venous network causes an increase in renal vascular resistance and a fall in renal blood flow. This can lead directly to a decline in glomerular filtration and a direct path to acute renal failure.

Elevated serum urate can contribute to renal damage even in the absence of crystal formation [100]. It has been shown that uric acid contributes to endothelial dysfunction in part by suppressing the synthesis of nitric oxide (NO), a signaling gas that relaxes smooth muscles, promoting vascular flow. Thus, uric acid can induce vascular constriction in the renal tubules, promoting a hypoxic state that induces an inflammatory response. This would work synergistically with tubular fibrosis to deplete oxygen supply to the tubular epithelial cells. Hyperuricemia in rats caused an increase in macrophage infiltration even in the absence of crystal formation [101]. Uric acid levels in humans are linked to preglomerular arterial disease [25]. Decrease in renal blood flow causes injury to the proximal tubules by depleting ATP, disruption of calcium homeostasis, and the generation of free radicals [102]. Damaged tubular cells are released into the tubular lumen causing obstruction.

ACTH

Adrenocorticotropic hormone (ACTH) is neuroprotective in chronic kidney disease, as well as in acute kidney disease [103-105]. Tumor necrosis factor α (TNF- α) is a key cytokine expressed in the inflammatory response. Injection of TNF- α into the kidney elicits massive cellular apoptosis in the tubules. The typical response pattern includes acute tubular necrosis, characterized by vacuolization of proximal tubular epithelium, epithelial necrosis, sloughing of tubular cells into the lumen, loss of the brush border, nuclear enlargement and prominent inflammatory infiltration. Remarkably, a dose of ACTH gel of 10 IU/kg greatly ameliorated these histological lesions [105].

Multiple studies have shown that Roundup suppresses the release of ACTH by the pituitary gland [106-108]. A study exposing rats to 10 mg/kg per day of Roundup for two weeks revealed reduced production of corticosterone by the adrenal glands, despite the fact that the ACTH receptors remained intact [106]. Exogenous treatment with ACTH rescued steroidogenesis in the exposed rats. They proposed that Roundup disrupts the hypothalamic-pituitary axis leading to reduced expression of ACTH by the pituitary gland. Cericato et al. have demonstrated that fish exposed to sublethal doses of glyphosate have an impaired capacity to raise cortisol levels in response to stress [107]. A later paper by the same authors showed that glyphosate's suppression of cortisol production in interrenal tissues in fish (corresponding to the adrenal glands in mammals) is caused by its disruption of the release of ACTH from the pituitary gland [108].

Addressing the MeN Epidemic

We have postulated that glyphosate is the cause of Mesoamerican nephropathy (MeN), with the synergistic involvement of several co-factors having a role in its progression to end-stage renal failure. Perhaps with the mounting evidence of glyphosate's toxic effects, the

elimination of the herbicide on sugarcane in Central America is not an unreasonable public health goal. In the meantime, is there something that can be done to halt the progressive deterioration of renal function in cane workers? MeN is an occupational disease [109]. So what would workplace intervention look like on a sugarcane plantation? It might include actions by management to: reduce agrochemical exposures; prevent dehydration and heat stress; recognize and treat rhabdomyolysis without the use of acetaminophen or NSAIDs; stop burning cane; record and publicly share data on the use of agricultural chemicals (what, when, where, how much); and acknowledge poverty as a social determinant of MeN by increasing wages and other worker support.

What else can be done? Climate change should be recognized as a co-factor in MeN [110-112]. The increase in temperatures in already hot places like the Pacific coastal plains in Central America impact MeN in at least two ways: more heat stress and dehydration. It should be noted that increasing ethanol production as a substitute for fossil fuels is problematic in the framework of MeN mitigation. Sugarcane is a common feedstock for ethanol production. For instance, in Brazil, the world's largest grower of sugarcane, the majority of harvested sugarcane is used to make ethanol [113,114]. The cost of increased cane production to meet global demand for ethanol is not only worker health but also the loss of land for small farmers, deforestation, and water pollution [115-117]. Unless the conditions for growing, managing, and harvesting sugarcane are changed to reflect our greater understanding of MeN, increasing sugarcane acreage to boost ethanol sales will also likely increase deaths from chronic kidney disease among cane workers.

Numerous studies about supportive therapies for acute kidney injury and CKD are available, but Mesoamerican nephropathy has not been slowed or stopped [118-120]. For example, in El Salvador and Nicaragua, from 1990 to 2009, male death rates from kidney failure increased 458% [121]. Very few patients in Central America with end-stage renal failure receive dialysis or kidney transplants [122]. The complex physiological processes that are part of MeN and the lack of consensus about its cause help contribute to poor health outcomes [87,123]. Nevertheless, the specific site of injury to the kidney in people with MeN and the mechanisms of harm caused by glyphosate give important clues to how cane workers – without access to advanced medical care and with limited finances – might treat renal assaults.

Intestinal fibrosis and tubular injury are clinical features of MeN [87,124-127]. Novel therapies that help prevent intestinal fibrosis and protect the tubules include heparin; ACTH gel; oxygen free radical scavengers such as ginseng, curcumin, alpha-lipoic acid (ALA), Vitamin E, and propofol; and trace elements such as selenium and zinc [70,105,128-131]. It should be noted that the National Kidney Foundation advises against the use of all herbal supplements [132]. Research opportunities abound for the clarification of advice with regard to the use of supplements for the treatment of kidney injuries, and also to address the inflammation and oxidative stress commonly associated with MeN.

Low-level light therapy (LLLT) may modulate chronic kidney disease progression [133]. LLLT seems especially promising because of its ease of use and low cost. It is also non-invasive and painless. In one animal study, LLLT had a protective effect on renal interstitial fibrosis [134]. Another study showed improved renal blood circulation in 58% of patients along with increased diuresis, and improved filtration and concentration functions [135]. In Brazil, the Federal University of Health Sciences of Porto Alegre has an on-going clinical trial looking at LLLT treatment for chronic kidney disease [136].

As with all disease prevention and treatment, diet is of critical importance. Probably the three most important interventions with regard to diet and MeN would be the elimination of glyphosate and reduction of fructose from the diet, and securing chemical and pathogen-free water [30,87,137-140]. The consumption of alcohol has been identified as a possible co-factor in MeN [22]. What may be particularly significant is the kind of alcohol consumed. Sanoff et al. showed that homemade liquor (lija) consumption in Nicaragua was associated with increased odds of having renal injury [22]. Homemade liquor does not always cause health problems, but it can under certain process or storage conditions [141]. If the liquor collected and used for drinking is from the beginning or the end of the distillation process, when the temperatures are not ideal for making ethanol, it can be poisonous. Toxicants such as pesticides and heavy metals can come from contaminated containers used in either the distillation process (for example, car radiators) or storage. Another issue is the proof of the liquor. Higher proof liquor has less water in it. It can exacerbate already critical dehydration problems. A treatment intervention that is unlikely to work is to tell people not to drink lija. What may instead have positive results is education about how to make homemade alcohol safer for consumption, along with frequent hydration with clean water during consumption.

A feasible large-scale experiment that could help determine glyphosate's role in CKDu would be to compare cane cutters with no occupational exposure to glyphosate with cutters with occupational exposure to the herbicide. It would be necessary to monitor other risk factors in the experiment, matching the work conditions as closely as possible between the two groups. Organic sugarcane is grown in the Americas, with the most acreage in Paraguay, Argentina, Cuba, Columbia, Mexico, Ecuador, and the United States (data on Brazil is unavailable) [142,143]. Disease surveillance of sugarcane cutters at organic sugarcane plantations could be compared to cane cutters that work in fields where glyphosate is used.

Conclusion

CKDu is a global disease of increasing prevalence. CKDu has been identified in Nicaragua, El Salvador, Guatemala, Honduras, Costa Rica, Panama, Mexico, Egypt, Sri Lanka and India, with markedly fewer cases in Cuba, Dominican Republic and Brazil, possibly because of access to better medical care for workers [10,142,144,145]. However, in Brazil, the largest producer of sugarcane in the world, it has been postulated that CKDu is either underdiagnosed or undertreated [146]. A number of known risk factors appear to contribute to chronic kidney disease in Mesoamerican agricultural workers, but they do not explain the meteoric rise of kidney failures. Glyphosate exposure not only damages the kidneys directly, but also can be predicted to increase the damaging effects of multiple other factors, most significantly urate synthesis from fructose, exposure to mycotoxins and metal toxicity. The health crisis among sugarcane workers on the Pacific coast of Central America can be addressed in numerous ways, but the action most likely to prevent end-stage renal failure is to stop using glyphosate on sugarcane.

We would like to close with a quote from an editorial by Dr. Andrew Campbell, who summarizes well our own feelings on this subject: "No one should be surprised that this chemical compound, the world's number one herbicide, glyphosate, can be toxic. We regularly add chemicals to our ecosystem only to find out years or decades later that we should have been more diligent in making sure all the effects of these chemicals had been studied. This is the time for all of us to read again Rachel Carson's "The Silent Spring" [148].

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