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Kidney Function, Self-Reported Symptoms, and Urine Findings in Nicaraguan Sugarcane Workers

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Abstract

Background An epidemic of CKD in Central America predominantly affects males working in certain industries, including sugarcane. Urinary tract infections are commonly diagnosed among men in Nicaragua, who often receive antibiotics and nonsteroidal anti-inflammatory drugs for urinary symptoms.

Methods We followed 251 male Nicaraguan sugarcane workers in seven job tasks over one harvest and measured urine dipstick parameters, kidney injury biomarkers, and eGFR. We administered a questionnaire about urinary symptoms, health-related behaviors, and medication history. We cultured urine in a subset of workers.

Results The study population was composed of factory workers (23%), cane cutters (20%), irrigators (20%), drivers (16%), agrichemical applicators (12%), seeders/reseeders (6%), and seed cutters (4%). The mean age of participants was 33.9 years, and mean employment duration was 10.1 years. Cane cutters reported higher proportions of urinary-related symptoms compared with agrichemical applicators, irrigators, and seeders/reseeders. Seed cutters were more likely to take antibiotics (22%), whereas drivers and seeders/reseeders were more likely to take pain medications (27% and 27%, respectively). Proteinuria was uncommon, whereas dipstick leukocyte esterase was relatively common, especially among cane cutters, seed cutters, and seeders/reseeders (33%, 22%, and 21% at late harvest, respectively). Dipstick leukocyte esterase at late harvest was associated with a 12.9 ml/min per 1.73 m^2 (95% CI, −18.7 to −7.0) lower mean eGFR and 2.8 times (95% CI, 1.8 to 4.3) higher mean neutrophil gelatinase-associated lipocalin. In general, workers who reported urinary-related symptoms had higher mean kidney injury biomarker levels at late harvest. None of the workers had positive urine cultures, including those reporting urinary symptoms and/or with positive leukocyte esterase results. Amoxicillin, ibuprofen, and acetaminophen were the most commonly used medications.

Conclusions Job task is associated with urinary symptoms and dipstick leukocyte esterase. Urinary tract infection is misdiagnosed based on leukocyte esterase, which may be an important predictor of kidney outcomes.

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Introduction

An epidemic of CKD of uncertain etiology, often referred to as either CKDu or Mesoamerican nephropathy (MeN), has been affecting Central America for more than two decades. Traditional risk factors for CKD, such as hypertension and diabetes, are not implicated in CKDu in this region (1–5). This disease most often affects younger men employed in certain industries, including agriculture, mining, and brickmaking (2,3,6–8). Nicaragua has one of the highest CKD mortality rates in the world, particularly among younger men (9). Possible causes include known and potential nephrotoxins, such as heavy metals, agrichemicals, infectious agents, nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, and other etiologies of intrinsic kidney injury, such as sequelae of volume-related acute tubular necrosis.

Patients with CKDu rarely exhibit high levels of proteinuria, but do appear to have elevated levels of tubular injury biomarkers, suggesting early tubulointerstitial damage (1–3,8,10–14), and kidney biopsy specimens show interstitial fibrosis and tubular atrophy (15–18). Hyperuricemia, dysuria, and sterile pyuria have also been reported in these populations (12,19,20). Interviews with physicians and pharmacists in two agricultural regions of Nicaragua indicate that patients frequently report symptoms consistent with urinary tract infections (UTIs; *e.g.*, dysuria, back pain) (21). In a sample of 61 Nicaraguan sugarcane workers, review of their medical records revealed that 69% received one or more UTI diagnoses, which were accompanied by urinalyses showing 75% had evidence of white blood cells, 35% had leukocyte casts, and 53%

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had crystalluria (22). A cross-sectional study among Costa Rican sugarcane workers found that harvesters were more likely than nonharvesters to experience dysuria once per week (28% versus 3%) (23), and a retrospective cohort study of Nicaraguan sugarcane workers reported that the odds of dysuria was 2.5-fold (95% CI, 1.6 to 4.0) higher in cane cutters compared with other field jobs (24). These findings suggest a relationship between urinary symptoms and job task. Dysuria is so common in Nicaragua that a colloquial term, *chistata*, has emerged to describe a set of symptoms including painful urination, burning during urination, and back pain (21). In El Salvador, the same common symptoms are referred to as *mal de orina*. Physicians in Nicaragua acknowledge they frequently prescribe NSAIDs and antibiotics for patients with these symptoms, and many report diagnosing a UTI in men based on urine dipstick results alone (21); they use urine cultures infrequently because of clinical protocols and limited resources. Positive urine dipstick tests, which test for presence of leukocyte esterase and nitrites, may suggest infection, but are not specific. Because UTIs are relatively uncommon in men compared with women, the routine diagnosis of UTIs in this predominantly male population at risk for CKDu is surprising and requires further investigation. The use of NSAIDs to treat dysuria may be a common practice throughout Central America, as indicated by a study in El Salvador that found that NSAID use (41%) and dysuria (39%) were common among a population largely working in agriculture (12).

It has been hypothesized that the frequent use of nephrotoxic medications for these UTI-like symptoms may lead to, or exacerbate, kidney damage (25). It has also been suggested that kidney injury in these populations could be the result of chronic volume depletion due to occupational conditions, which could result in crystal-related symptoms due to high concentration of urinary urates (26,27). Diuretics are commonly prescribed to treat *chistata* (21), which could further increase volume depletion, thereby resulting in higher concentrations of urinary urates and other substances during the volume challenge experienced during heavy manual labor in excessive heat. Kidney damage could also result from the combination of these two pathways, along with other nephrotoxic exposures (*e.g.*, agrichemicals, heavy metals).

The objectives of this study, conducted among male Nicaraguan sugarcane workers, were as follows: (*1*) to assess differences in self-reported symptoms and urine dipstick results across job categories; (*2*) to determine the associations among self-reported symptoms, urine dipstick results, late-harvest kidney function, and kidney injury biomarkers; (*3*) to describe patterns of medication use; and (*4*) to determine whether workers with UTI-like symptoms and positive urine leukocyte esterase results have positive urine cultures.

Materials and Methods

Study Participants

The study population and data collection methods have been described previously (13,28). Briefly, during October–December 2010, at the beginning of the harvest season ("preharvest"), sugarcane workers in Nicaragua were recruited and data were collected after a screening and hiring process conducted by the employer. Job applicants with serum creatinine ≥1.4 mg/dl were not hired and were, therefore, not included in the study population. A second round of data collection occurred near the end of the harvest season ("late harvest"), during March–May 2011, among a subset of workers selected by convenience. Of the workers who participated in both rounds of data collection (n=506), a random sample (n=284) of workers was selected for analyses, after excluding workers with more than one job and workers in certain job categories (*e.g.*, maintenance workers, machine operators). This sample was primarily male (88%). The 33 women were not equally distributed among the job categories—two factory workers, ten seed cutters, and 21 seeders/reseeders—and did not include any cane cutters, the work category previously identified to be associated with the greatest risk of CKDu. Thus, the analyses in this study were restricted to men only (n=251). All participants were at least 18 years old.

The final population represented workers from seven different job categories: drivers, factory workers, cane cutters, irrigators, agrichemical applicators, seed cutters, and seeders/reseeders. Factory workers are employees of the sugarcane company who perform a variety of jobs, including operators, mechanics, and technicians. They typically work 12-hour shifts. Cane cutters are contracted laborers who use machetes to cut the sugarcane at the base and stack the stalks into a pile for collection. Cane cutters typically cut 4–6 tons of sugarcane per day over a 6-hour shift, and are paid based on the amount of sugarcane cut each day. Irrigators are employees of the sugarcane company who manually divert water from main water conductors into the furrows of individual fields using sticks and plastic or removal/addition of soil. They typically handle 1000 gallons/field per day over 9-hour shifts. Agrichemical applicators are also contracted and apply agrichemicals (primarily herbicides) to the ground and base of the sugarcane using backpack pumps (the majority of which require manual force to control the pressure). The most commonly used herbicide mixture is 2,4-dichlorophenoxyacetic acid, terbutryn, and ametryn. Applicator shift durations vary between 5 and 12 hours per day. Seed cutters are contracted laborers who use machetes to cut the sugarcane into 20- to 22-inch pieces and tie them together into packages (typically preparing 80–100 packages per day). They are paid by the package and work up to 8 hours per day. Seeders/reseeders are contracted laborers who distribute the cut sugarcane stalks evenly in 204-m furrows and cover them with soil using shovels or hoes. They typically plant two to four furrows a day over a 5- to 6-hour shift and are paid by the furrow.

Data Collection

At preharvest, workers provided blood and urine samples and were administered questionnaires, by trained interviewers, about their work history and demographics. Similar data were collected at late harvest, with additional questions regarding symptoms experienced, hydration practices, and alcohol consumption. Symptoms included abdominal, back, and flank pain; burning or pain during urination; periods of frequent urination; fever or chills; and *chistata*. Workers also reported whether they sought medical treatment during the harvest season and whether they were diagnosed with a UTI during the harvest season. Separate questions asked about general use of pain medication and antibiotics (*i.e.*, yes/no in previous 3 months) versus specific treatments recommended by health professionals and used by workers (discussed in further detail under Medications Recommended and Used).

Serum creatinine was measured at the National Diagnostic and Reference Center (Managua, Nicaragua) using a kinetic-rate Jaffe method (traceable to isotope dilution mass spectrometry). eGFR was calculated using the CKD–Epidemiology Collaboration equation (29). Urine creatinine, albumin, neutrophil gelatinase-associated lipocalin (NGAL), IL-18, and *N*-acetyl-β-D-glucosaminidase (NAG) were analyzed at the Division of Nephrology and Hypertension at the Cincinnati Children's Hospital Medical Center (Cincinnati, OH). Urine creatinine was measured using immunoturbidimetry. Albumin was measured using a colorimetric modification of the Jaffe reaction. Albumin-creatinine ratio (ACR) was calculated by dividing urine albumin by urine creatinine. NGAL and IL-18 were measured with commercially available ELISA kits (Bioporto, Gentofte, Denmark; MBL International, Woburn, MA). NAG was measured with a colorimetric assay (Roche Diagnostics, Basel, Switzerland). Detection limits were 1.3 mg/L for urine albumin, 1.6 pg/ml for NGAL, 4 pg/ml for IL-18, and 0.003 U/L for NAG. Urine dipstick analyses were performed using a Combur 10UX dipstick (Roche Diagnostics) and Urisys 1100 strip reader (Roche Diagnostics) (13,28).

The institutional review boards at the Boston University Medical Center and the Nicaraguan Ministry of Health approved the protocols for this study. All participants provided informed consent before their participation.

Urine Cultures

During late harvest, urine samples were collected from 70 workers for urine cultures, which were initiated within 3 hours of specimen collection at National Autonomous University of Nicaragua at León. This subset of workers was selected based on combinations of urinary symptoms in the past 24 hours and/or a positive leukocyte esterase test result from a dipstick analysis (see Supplemental Appendix 1 and Supplemental Table 1 for selection criteria and demographic information). Positive cultures were defined as either having a growth of at least 100,000 CFU/ml, or having a growth of at least 20,000 CFU/ml in the presence of positive urine dipstick for nitrates or leukocytes.

Statistical Analyses

Summary statistics were calculated for all participants (n=251). For normally distributed variables, the mean and SD were calculated. For log-normally distributed variables, the geometric mean and geometric SD were calculated. Histograms were used to assess the normality of continuous outcome variables. All urine dipstick results were dichotomized into any positive (*e.g.*, 1+, 2+, 3+) versus negative to avoid small counts.

To examine differences in self-reported symptoms and urine dipstick parameters between job tasks, chi-squared tests for crude analyses and logistic regression models to adjust for age and employment duration were used. Factory workers were used as the reference population. For rare outcomes, the Firth bias correction was used to avoid quasi-complete separation (30). Additional analyses were conducted to examine the differences between field workers and nonfield workers by combining drivers and factory workers into a "nonfield workers" category, and combining cane cutters, irrigators, agrichemical applicators, seed cutters, and seeders/reseeders into a "field workers" category.

To examine crude associations among self-reported symptoms, urine dipstick results, and kidney outcomes (kidney function [eGFR] and kidney injury biomarkers [NGAL, NAG, IL-18, ACR]), mean differences were calculated and two-sample t tests (using equality of variances F tests to determine whether equal variances could be assumed) were applied. Adjusted mean differences—controlling for age, employment duration, and job category—were calculated using multivariable linear regression models. For all models with injury biomarkers as the dependent variable, we also adjusted for urine creatinine concentration (except for ACR, which is normalized to urine creatinine). The injury biomarkers were natural-log transformed to account for non-normal distributions; therefore, the parameter estimates reported are relative mean differences derived from exponentiation of the parameter estimates. For models predicting late-harvest eGFR, we truncated all eGFR values >120 ml/min per 1.73 m^2 at 120 ml/min per 1.73 m^2 because of the imprecision of GFR estimates at these high levels.

Medications Recommended and Used

For workers who reported receiving treatment recommendations or prescriptions from medical care providers, we asked them to list these prescriptions and/or treatments, along with the specific antibiotics and pain medications they actually took in the 3 months before the late-harvest data collection. Because these answers contain large percentages of missing values or instances when workers could not remember the name of a medication, results provided for these questions are descriptive only. Questions pertaining to general use of antibiotics and pain medication (*i.e.*, yes/no in prior 3 months), seeking treatment, and being diagnosed with a UTI were not subject to the same levels of missing data and were, therefore, included in our statistical analyses.

All analyses were conducted using SAS version 9.4 (SAS Statistical Software, Cary, NC).

Results

Study Cohort Characteristics

Our study population was primarily composed of factory workers (23%), cane cutters (20%), irrigators (20%), drivers (16%), and agrichemical applicators (12%). There were relatively few seed cutters (4%) and seeders/reseeders (6%) after excluding female workers from these analyses. The mean age of participants was 33.9±10.5 years (Table 1). There were differences in mean age by job category, with drivers being the oldest, followed by factory workers and agrichemical applicators. Drivers, factory workers, agrichemical applicators, irrigators, and seeders/reseeders worked for the sugarcane company longer than cane cutters and seed cutters—in many cases, more than two or three times as long. See Supplemental Appendix 2 and Supplemental Tables 2 and 3 for data on female participants.

Differences in Symptoms, Health-Related Behaviors, and Urine Dipstick by Job Category

Cane cutters, compared with all other jobs, reported higher proportions of the urinary symptoms, except *chistata* (Table 2). Agrichemical applicators generally reported the lowest proportions of these symptoms. These findings generally remained consistent after adjusting for age and employment duration (Table 3).

Seed cutters were more likely to report using antibiotics in the 3 months before the late-harvest data collection, whereas drivers and seeders/reseeders were more likely to report taking pain medications (Table 2). Irrigators were the least likely to seek medical treatment during this period.

Leukocyte esterase and proteinuria at preharvest were relatively uncommon (Table 2). Urinary nitrites were very uncommon (n=1; not shown). Leukocyte esterase at late harvest was more common among cane cutters, seed cutters, and seeders/reseeders (33%, 22%, and 21%, respectively) compared with factory workers (2%).

When comparing self-reported symptoms, dipstick parameters, health behaviors, and diagnoses, minimal differences were found between field workers and nonfield workers (not shown). Odds of symptoms and dipstick parameters were slightly higher among field workers. Late-harvest leukocyte esterase results were the only substantial difference between the two groups, with field workers being more likely to have positive leukocyte esterase results (odds ratio, 8.34; 95% CI, 1.88 to 37.04).

Associations with Late-Harvest Kidney Injury and Kidney Function

In unadjusted analyses, late-harvest eGFR was 5.3 ml/min per 1.73 m^2 (95% CI, −12.4 to 1.8) lower for workers who reported taking pain medications for at least 3 days in the prior 3 months; 10.6 ml/min per 1.73 m^2 (95% CI, −23.0 to 1.9) lower for workers with hematuria at late harvest; and 3.1 ml/min per 1.73 m^2 (95% CI, −8.3 to 2.1) lower for workers reporting abdominal, back, or flank pain (Table 4). Late-harvest eGFR was 14.1 ml/min per 1.73 m^2 (95% CI, −37.5 to 9.3) lower for workers with proteinuria at late harvest; however, these findings are based on few events (n=8). Large differences in eGFR were also found for workers with positive leukocyte esterase at late harvest (mean difference, −13.3 ml/min per 1.73 m^2; 95% CI, −25.0 to −1.6). After adjusting for age, employment duration, and job category, these differences in mean eGFR were largely attenuated, except for leukocyte esterase and hematuria at late harvest, which were still strongly associated with a lower eGFR (mean difference, −12.9 [95% CI, −18.7 to

Table 1. Participant characteristics, late-harvest eGFR, and late-harvest kidney injury biomarker results by job category (n=251)

Characteristics	Overall	Nonfield Workers		Field Workers				
		Drivers	Factory Workers	Cane Cutters	Irrigators	Agrichemical Applicators	Seed Cutters	Seeders/ Reseeders
Total, N (%)	251 (100)	41 (16)	57 (23)	51 (20)	49 (20)	29 (12)	9 (4)	15 (6)
Age, yr								
Mean	33.9	40.9	36.3	30.5	30.3	34.7	27.1	31.7
Median	31	41.0	36	28.0	28.0	35.0	27	29
SD	10.5	11.2	9.9	10.6	8.8	8.2	3.7	10.0
Range	18–63.5	24.0–60.0	20–57	18.0–63.5	19.0–48.0	21.0–51.0	23–34	19–56
Employment duration, yr								
Mean	10.1	14.4	14.2	3.6	9.7	12	2	7.3
Median	7	13.0	13	1.0	7.0	12.0	1	5
SD	9.2	8.9	10.7	5.3	8.0	8.0	2.3	6.2
Range	0–40	1.0–35.0	0.08–40	0–27.0	0–32.0	0–30.0	0–6	2–22
eGFR (ml/min per 1.73 m^2)								
Mean	112.4	110.2	114.8	108.2	115.5	114.4	112.3	110.38
SD	19.0	14.2	16.2	26.3	16.9	13.7	20.9	24.1
Range	28.9–180.9	78.3–139.3	76.2–180.9	28.9–150.2	45.7–142.7	81.8–138.8	63.3–128.6	56.8–143.7
NAG (U/g)								
GM	0.90	0.68	0.60	1.5	0.90	0.93	0.63	1.6
GSD	2.8	2.3	2.8	2.1	3.5	2.3	3.5	3.0
NGAL (μg/g)								
GM	10.4	7.5	6.8	19.3	14.7	6.9	6.2	15.3
GSD	3.4	2.2	4.3	2.9	3.3	3.2	1.7	2.9
IL-18 (ng/g)								
GM	8.8	9.9	6.4	12.6	7.5	8.5	5.4	14.8
GSD	3.1	2.9	3.1	3.5	2.8	3.0	2.7	3.1
ACR (mg/g)								
GM	2.4	2.0	1.6	2.0	4.2	2.7	1.0	6.6
GSD	3.6	4.4	3.1	2.8	3.6	3.2	2.9	3.3

Urine analytes are normalized to the urine creatinine concentration. NAG, N-acetyl-β-D-glucosaminidase; GM, geometric mean; GSD, geometric SD; NGAL, neutrophil gelatinase-associated lipocalin; ACR, albumin-creatinine ratio.

Table 2. Self-reported urinary symptoms and health-related behaviors in the previous 3 mo by job category

Symptoms, Behaviors, Diagnoses, and Dipstick Results	Nonfield Workers		Field Workers				
	Factory Workers (Reference)	Drivers	Cane Cutters	Irrigators	Agrichemical Applicators	Seed Cutters	Seeders/ Reseeders
Total, *N*	57	41	51	49	29	9	15
Symptoms, prior 3 mo (%)[a]							
Abdominal, back, flank pain	28	29	39	20	17	0	20
Burning/pain during urination	12	7	23	8	4	22	7
Frequent urination	9	10	18	6	0	0	7
Fever or chills	11	7	32	4	0	11	13
Chistata[b]	28	27	55	27	24	67	27
Health-related behaviors and diagnoses, prior 3 mo (%)[a]							
Taken antibiotics	19	12	9	10	7	22	13
Taken pain medication ≥3 d	11	27	16	8	4	11	27
Sought medical treatment	18	12	21	6	14	22	33
Diagnosed with a UTI	5	3	2	2	4	0	7
Dipstick parameters, preharvest (%)							
Positive leukocyte esterase	5	3	10	2	4	0	0
Positive proteinuria	2	0	6	4	0	0	0
Dipstick parameters, late harvest (%)							
Positive leukocyte esterase	2	3	33	8	4	22	21
Positive proteinuria	4	3	2	6	0	0	7
Positive blood	9	5	6	10	7	11	21

UTI, urinary tract infection.
[a]Workers reported symptoms, health-related behaviors, and recent UTI diagnoses during late-harvest data collection.
[b]*Chistata* is a colloquial term that describes a set of symptoms including painful urination, burning during urination, and back pain.

−7.0] and −8.5 ml/min per 1.73 m^2 [95% CI, −15.0 to −2.0], respectively).

In unadjusted analyses, workers who reported having experienced fever or chills (prior 3 months) had >50% greater mean NGAL and NAG values at late harvest compared with those not experiencing fever or chills (Table 4). These were both slightly attenuated after adjustment. Proteinuria at preharvest and late harvest were associated with large relative increases in all four injury biomarkers, in both unadjusted and adjusted analyses (Table 4), however, these are based on relatively few events (n=6 for preharvest, n=8 for late harvest). Positive leukocyte esterase at late harvest, but not preharvest, was associated with higher NGAL levels (adjusted relative mean, 2.8; 95% CI, 1.8 to 4.3) and lower IL-18 levels (adjusted relative mean, 0.5; 95% CI, 0.3 to 0.7). There is some suggestion that self-reported use of antibiotics and pain medications are associated with higher levels of NGAL, NAG, and IL-18, even after adjustment for potential confounders (Table 4). Workers who reported experiencing *chistata* and periods of frequent urination had higher relative mean NGAL and IL-18 levels at late harvest, respectively, even after adjustment. Workers reporting periods of frequent urination or abdominal, back, or flank pain had higher mean ACR at late harvest.

Medications Recommended and Used

Of the workers who reported seeking and receiving treatment recommendations from medical care providers (n=38), over a third (37%) reported that the recommended treatment was an analgesic. Fewer reported that their medical care provider recommended an antibiotic (13%). Four workers said their care provider recommended a change in diet and hydration. Eleven workers (29%) said they did not remember the name of the treatment. Among the workers who reported taking an antibiotic in the 3 months before late harvest (n=31), the most commonly reported antibiotic taken was amoxicillin (n=5; 16%), followed by azithromycin (n=3; 10%). Cephalexin and tetracycline were reported by one worker each. Five workers did not remember the name of the antibiotic they took, and 15 (48%) did not answer the question. Not all antibiotics were taken for UTI symptoms. A few workers reported that antibiotics were taken for other ailments (*e.g.*, foot infection, influenza, sore throat). Of the workers who reported taking a pain medication for at least 3 days in the 3 months before the late harvest (n=34), 24% reported taking ibuprofen and 12% reported taking acetaminophen. One worker did not remember the name of the pain medication and 20 (59%) did not answer the question.

Table 3. Adjusted association of symptoms and clinical findings with job task

Symptoms and Findings	Odds Ratios (95% Confidence Intervals)						
	Nonfield Workers		Field Workers				
	Factory Workers	Drivers	Cane Cutters	Irrigators	Agrichemical Applicators	Seed Cutters	Seeders/ Reseeders
Symptoms, prior 3 mo[a]							
Abdominal, black, flank pain	Reference	1.22 (0.49 to 3.02)	2.28 (0.89 to 5.82)	0.69 (0.28 to 1.73)	0.60 (0.20 to 1.82)	0.18 (0.01 to 3.94)	0.84 (0.21 to 3.36)
Burning or pain during urination	Reference	0.67 (0.16 to 2.81)	2.68 (0.79 to 9.07)	0.60 (0.16 to 2.27)	0.27 (0.03 to 2.28)	2.46 (0.37 to 16.3)	0.55 (0.06 to 5.08)
Periods of frequent urination	Reference	1.23 (0.33 to 4.62)	2.62 (0.72 to 9.61)	0.72 (0.17 to 3.00)	0.17 (0.01 to 3.12)	0.57 (0.02 to 13.8)	1.07 (0.15 to 7.67)
Any fever or chills	Reference	0.75 (0.19 to 2.99)	4.69 (1.42 to 15.5)[b]	0.44 (0.10 to 2.05)	0.14 (0.01 to 2.60)	1.73 (0.21 to 14.4)	1.68 (0.32 to 8.78)
Chistata[c]	Reference	1.13 (0.45 to 2.84)	3.24 (1.29 to 8.17)[b]	0.79 (0.33 to 1.91)	0.80 (0.29 to 2.27)	4.67 (0.98 to 22.3)	0.88 (0.24 to 3.28)
Health-related behaviors and diagnoses, prior 3 mo[a]							
Taken antibiotics	Reference	0.68 (0.21 to 2.18)	0.54 (0.14 to 2.02)	0.46 (0.14 to 1.48)	0.32 (0.07 to 1.58)	1.49 (0.25 to 9.10)	0.72 (0.14 to 3.83)
Taken pain medications >3 d	Reference	2.93 (0.96 to 8.96)	1.96 (0.54 to 7.16)	0.87 (0.23 to 3.38)	0.32 (0.04 to 2.81)	1.43 (0.14 to 14.7)	3.63 (0.83 to 15.9)
Sought medical treatment	Reference	0.58 (0.18 to 1.90)	1.56 (0.50 to 4.87)	0.37 (0.09 to 1.48)	0.81 (0.23 to 2.89)	2.01 (0.33 to 12.4)	2.93 (0.77 to 11.1)
Diagnosed with a UTI	Reference	0.40 (0.06 to 2.95)	0.41 (0.05 to 3.39)	0.57 (0.08 to 4.03)	0.81 (0.11 to 5.75)	0.87 (0.03 to 23.4)	1.41 (0.17 to 11.9)
Dipstick parameters, preharvest							
Leukocyte esterase	Reference	0.70 (0.10 to 4.82)	2.85 (0.56 to 14.7)	0.53 (0.07 to 3.80)	0.88 (0.12 to 6.33)	1.24 (0.04 to 34.7)	0.63 (0.03 to 14.0)
Proteinuria	Reference	0.43 (0.02 to 9.68)	4.32 (0.48 to 39.1)	2.69 (0.34 to 21.4)	0.70 (0.03 to 17.0)	3.41 (0.09 to 126)	1.71 (0.06 to 46.2)
Dipstick parameters, late harvest							
Leukocyte esterase	Reference	1.45 (0.15 to 14.0)	15.4 (2.55 to 92.4)[b]	3.25 (0.50 to 21.3)	1.83 (0.19 to 18.1)	9.59 (0.97 to 95.1)	9.86 (1.28 to 76.0)[b]
Proteinuria	Reference	1.00 (0.12 to 8.28)	2.38 (0.23 to 24.4)	2.82 (0.48 to 16.8)	0.53 (0.02 to 11.8)	4.73 (0.14 to 164)	5.78 (0.56 to 59.6)
Blood	Reference	0.44 (0.08 to 2.49)	0.75 (0.14 to 3.91)	1.49 (0.38 to 5.76)	0.81 (0.15 to 4.50)	1.80 (0.16 to 19.9)	3.16 (0.60 to 16.6)

Odds ratios (95% CI) for self-reported symptoms and dipstick parameters (preharvest and late harvest) compared with reference group (factory workers), adjusting for age and employment duration (n=244 for symptoms and behaviors/treatments, n=247 for dipstick except blood, n=246 for blood at late harvest, n=243 for UTI diagnoses). UTI, urinary tract infection.
[a]Workers reported symptoms, health-related behaviors, and recent UTI diagnoses during late-harvest data collection.
[b]$P<0.05$.
[c]*Chistata* is a colloquial term that describes a set of symptoms including painful urination, burning during urination, and back pain.

Urine Cultures

Of the 70 workers who gave urine samples for culturing (demographics provided in3 Supplemental Table 1), 27% reported urinary symptoms in the prior 24 hours (n=19) and 31% had a positive leukocyte esterase test result from the dipstick analyses (n=22). A small portion of these were both positive for leukocyte esterase and reported symptoms in the last 24 hours (n=7). Approximately half of the subset (49%) were neither positive for leukocyte esterase nor reported experiencing recent symptoms (n=34) and, therefore, represented a negative control. Finally, five participants (7%) had missing symptom data for the prior 24 hours—three were positive for leukocyte esterase and two were negative. Of these 70 workers, none had positive urine culture results.

Discussion

In a cohort of male Nicaraguan sugarcane workers followed across one harvest season, we identified differences in self-reported urinary symptoms, urine dipstick results, and health-related behaviors by job category. Cane cutters reported higher proportions of urinary-related symptoms, whereas agrichemical applicators and irrigators generally reported lower proportions. Leukocyte esterase was relatively common, particularly at late harvest and among cane cutters, seeders/reseeders, and seed cutters (range, 21%–33% at late harvest). Late-harvest leukocyte esterase was associated with lower eGFR and higher NGAL. Late-harvest hematuria was associated with lower eGFR and higher NAG and ACR, which could suggest that crystalluria is present and may be contributing to symptoms. In general, workers who reported experiencing urinary-related symptoms had higher mean kidney injury biomarker levels at late harvest.

This study logically follows our prior study—which demonstrated an association between certain job tasks and higher levels of kidney injury biomarkers and lower late-harvest eGFR—by correlating these jobs with a higher symptom burden and more frequent findings of positive leukocyte esterase on urine dipstick. This is important because the disease is currently believed to be asymptomatic at early stages, with no established early indicators of disease. *Chistata* and other urinary symptoms may be related to crystalluria caused by dehydration and not UTIs. We found urinary nitrites to be uncommon (0.4%), and all 70 urine cultures were negative, indicating that dipstick leukocyte esterase in this study was not a marker of a UTI in men, which suggests a different source of kidney pathology than infection.

This finding appears to be supported by other research: all 12 urine cultures conducted in a study by Fischer *et al.* (31) were negative, and all patients with CKD were negative for nitrites. Sterile pyuria can be attributed to a number of different causes, including sexually transmitted infections, viral or fungal infections, parasitic diseases, interstitial nephritis from medications, or other causes of cystitis (32,33). In this population, reported use of pain medications and antibiotics were weakly associated with leukocyte esterase, in both crude and adjusted analyses. Although analgesics were commonly recommended to workers who sought medical treatment, relatively few male workers sought treatment in the first place (16%). It is worth noting that, during the duration of this study, participants were able to access the employer-provided healthcare clinic at no cost, because it is funded by the country's social security fund. Ibuprofen, an NSAID, was the most common pain medication reported among workers who used pain medications, but this represents very few workers in total. Similarly, few workers reported taking an antibiotic, and among those who did, there was a wide variety of antibiotics used. These findings seem to indicate that NSAIDs and antibiotics may not be the cause of sterile pyuria in this population, but better data on medication history are needed for a more robust analysis of this hypothesis. Given the limited biopsy series in MeN/CKDu, we suspect that NSAID and antibiotic use are not causing interstitial nephritis, but are rather being used to treat symptoms that are associated with increased MeN/CKDu risk.

There are aspects of our study that limit the interpretation and generalizability of our findings. Regarding data collection, the data are potentially subject to both nondifferential and differential misclassification, and differential loss to follow-up, because workers who were not available for late-harvest data collection may have differed from the entire study population at preharvest. Workers had trouble recalling specific names of medications they were prescribed or took during the study period, which limited data analysis. The study design was limited to changes across a single harvest season, limiting ability to draw conclusions about longer-term kidney function decline. The categorization of some of the symptoms, including *chistata*, is somewhat subjective and, therefore, may differ between workers and introduce misclassification. The sample sizes in a few of the job categories were relatively small and may have reduced our power to detect differences. Lastly, it is possible the criteria we used for assessing positive urine cultures were too strict (34,35).

The prediction of late-harvest eGFR and tubular injury biomarkers using late-harvest urine dipstick parameters (late-harvest dipstick leukocyte esterase, protein, and blood) should be interpreted with caution because these are cross-sectional analyses, which prevent us from determining whether proteinuria and dipstick leukocyte esterase are precursors or sequelae of kidney damage. The results presented in Table 4 should generally be considered as exploratory and require confirmation. However, our findings regarding the prevalence of symptoms, leukocyte esterase, and proteinuria are generally supported by other studies (1–4,6,12,23). We also suspect there may be some uncontrolled confounding in our models related to occupational exposures or willingness to seek medical care.

In conclusion, we found that leukocyte esterase and *chistata* were common among workers involved in strenuous field work, like cane cutting, generally correlating with workers who were found to have increased tubular injury biomarkers and larger crossharvest eGFR declines in previous studies. We found no evidence of UTIs in male workers, despite the urinary symptoms and positive leukocyte esterase results. These findings support the hypothesis that MeN/CKDu in this region is related to occupation, perhaps through recurrent exposure to heat stress and volume depletion, and that UTIs are likely not involved in the disease etiology. Our urine culture findings also indicate that urine

Table 4. **Associations between symptoms and positive urine dipstick results and kidney function and kidney injury**

Symptoms and Results	Number of Events (*N*)	Mean Difference (95% CI)		Relative Means (95% CI)							
		eGFR		NGAL[b]		NAG[b]		IL-18[b]		ACR	
		Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]	Crude	Adjusted[a]
Symptoms, prior 3 mo[c,d]											
Abdominal, back, flank pain	63	−3.1 (−8.3 to 2.1)	−2.3 (−6.5 to 1.9)	1.2 (0.9 to 1.7)	1.2 (0.8 to 1.6)	1.3 (0.9 to 1.7)	1.2 (0.9 to 1.6)	1.0 (0.7 to 1.3)	0.9 (0.7 to 1.2)	1.3 (0.9 to 1.8)	1.3 (0.9 to 1.8)
Burning or pain during urination	28	3.0 (−1.6 to 7.6)	3.7 (−2.1 to 9.4)	1.5 (1 to 2.3)	1.4 (0.9,2.1)	1.1 (0.7 to 1.7)	1.0 (0.7 to 1.6)	1.3 (0.9 to 1.9)	1.2 (0.8 to 1.8)	1.0 (0.6 to 1.7)	1.1 (0.7 to 1.8)
Periods of frequent urination	21	−1.4 (−8.5 to 5.7)	0.2 (−6.3 to 6.7)	1.3 (0.8 to 2.1)	1.1 (0.7 to 1.8)	0.8 (0.5 to 1.3)	0.7 (0.5 to 1.2)	1.4 (0.9 to 2.2)	1.3 (0.8 to 2)	1.3 (0.7 to 2.3)	1.3 (0.8 to 2.3)
Any fever or chills	28	−2.1 (−8.3 to 4.1)	1.2 (−4.8 to 7.1)	1.5 (1 to 2.4)	1.2 (0.8 to 1.9)	1.8 (1.2 to 2.8)[e]	1.5 (1 to 2.2)	1.2 (0.8 to 1.8)	1.0 (0.7 to 1.5)	1.0 (0.6 to 1.6)	1.0 (0.6 to 1.7)
Chistata[f]	81	1.7 (−2.6 to 5.9)	1.4 (−2.5 to 5.4)	1.4 (1 to 1.8)[e]	1.3 (1 to 1.7)	1.2 (0.9 to 1.6)	1.1 (0.9 to 1.5)	1.2 (0.9 to 1.5)	1.1 (0.9 to 1.5)	0.8 (0.6 to 1.2)	0.9 (0.6 to 1.2)
Health-related behaviors and diagnoses, prior 3 mo[c,d]											
Taken antibiotics	31	−0.4 (−6.4 to 5.6)	−1.3 (−6.8 to 4.1)	1.1 (0.7 to 1.7)	1.2 (0.8 to 1.9)	1.3 (0.9 to 2)	1.5 (1 to 2.2)[e]	1.1 (0.8 to 1.6)	1.2 (0.8 to 1.7)	1.1 (0.7 to 1.8)	1.2 (0.7 to 1.8)
Taken pain medications >3 d	34	−5.3 (−12.4 to 1.8)	−2.8 (−8.2 to 2.5)	1.4 (0.9 to 2)	1.3 (0.9 to 1.9)	1.5 (1 to 2.3)[e]	1.4 (1 to 2.1)	1.5 (1.1 to 2.2)[e]	1.4 (1 to 2)	0.7 (0.5 to 1.2)	0.7 (0.5 to 1.1)
Dipstick parameters, preharvest[g]											
Leukocyte esterase	11	−2.7 (−12.2 to 6.9)	−1.8 (−10.6 to 7.0)	1.6 (0.8 to 3.3)	1.5 (0.8 to 2.9)	1.5 (0.8 to 2.9)	1.3 (0.7 to 2.5)	1.3 (0.7 to 2.5)	1.3 (0.7 to 2.3)	1.0 (0.5 to 2.2)	1.1 (0.5 to 2.3)
Proteinuria	6	−0.9 (−13.7 to 11.9)	2.8 (−8.9 to 14.5)	6.7 (2.7 to 16.2)[e]	4.9 (2.1 to 11.6)[e]	3.8 (1.6 to 9.1)[e]	3.0 (1.3 to 6.7)[e]	3.0 (1.3 to 6.6)[e]	3.1 (1.4 to 6.9)[e]	5.7 (2.1 to 15.7)[e]	5.5 (2.1 to 14.4)[e]
Dipstick parameters, late harvest[g,h]											
Leukocyte esterase	29	−13.3 (−25.0 to −1.6)[e]	−12.9 (−18.7 to −7.0)[e]	3.4 (2.2 to 5.1)[e]	2.8 (1.8 to 4.3)[e]	1.5 (1 to 2.2)	1.0 (0.7 to 1.6)	0.6 (0.4 to 0.9)[e]	0.5 (0.3 to 0.7)[e]	1.0 (0.6 to 1.6)	0.9 (0.6 to 1.5)
Proteinuria	8	−14.1 (−37.5 to 9.3)	−10.9 (−21.1 to −0.7)[e]	3.7 (1.7 to 8.1)[e]	3.0 (1.4 to 6.6)[e]	2.5 (1.2 to 5.5)[e]	2.1 (1 to 4.3)	2.5 (1.3 to 5.1)[e]	3.1 (1.5 to 6.3)[e]	12.4 (5.3 to 28.9)[e]	9.4 (4.2 to 21.4)[e]
Blood	21	−10.6 (−23.0 to 1.9)	−8.5 (−15.0 to −2.0)[e]	0.9 (0.5 to 1.4)	0.8 (0.5 to 1.3)	1.6 (1 to 2.7)[e]	1.5 (0.9 to 2.3)	1.0 (0.6 to 1.5)	1.0 (0.7 to 1.6)	1.7 (1 to 3)	1.6 (0.9 to 2.7)

NGAL, neutrophil gelatinase-associated lipocalin; NAG, *N*-acetyl-β-D-glucosaminidase; ACR, albumin-creatinine ratio.
[a]Adjusted for age, employment duration, and job category.
[b]All crude and adjusted models predicting NGAL, NAG, and IL-18 were additionally adjusted for urinary creatinine.
[c]Reference was workers not reporting symptoms or health-related behaviors.
[d]Workers reported symptoms and health-related behaviors during late-harvest data collection.
[e]$P<0.05$.
[f]*Chistata* is a colloquial term that describes a set of symptoms including painful urination, burning during urination, and back pain.
[g]Reference was workers with negative dipstick results.
[h]Cross-sectional analyses.

dipstick analyses and symptom reporting alone are not adequate for diagnosing UTIs among males in this population. These findings were communicated with the participants' employer and the physicians at the employer healthcare clinic. Patient education on hydration and healthy urine color is now provided.

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Author Contributions

J. Amador, D. Brooks, J. Kaufman, R. Laws, D. López-Pilarte, M. McClean, O. Ramirez-Rubio, M. Scammell, and D. Weiner conceptualized the study; J. Amador, D. Brooks, J. Kaufman, D. López-Pilarte, M. McClean, Z. Petropoulos, O. Ramirez-Rubio, M. Scammell, and D. Weiner were responsible for methodology; J. Amador, R. Laws, D. López-Pilarte, and O. Ramirez-Rubio were responsible for data curation; D. Brooks, M. McClean, and M. Scammell provided supervision; Z. Petropoulos was responsible for formal analysis and wrote the original draft; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.K3602020000339/DCSupplemental.

Supplemental Appendix 1. Selection criteria for urine culture analyses.

Supplemental Appendix 2. Analyses of female workers (n=33).

Supplemental Table 1. Participant characteristics for the urine culture subset compared to all participants.

Supplemental Table 2. Participant characteristics and late-zafra biomarker results by job category among females.

Supplemental Table 3. Self-reported urinary symptoms and health-related behaviors in the previous 3 months by job category among females.

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