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Sugarcane Workweek Study: Mechanisms Underlying Daily Changes in Creatinine

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Chronic kidney disease of unknown origin (CKDu) is an epidemic that has resulted in tens of thousands of deaths among workers in Latin America.[1] It has been hypothesized that work, especially among sugarcane harvesters, contributes to the progression of disease through recurrent clinical and subclinical acute kidney injury.[2-5] In a previous study, we observed that among the same cohort of Guatemalan sugarcane harvesters, subgroups experienced differing degrees of daily changes in creatinine. Workers with the largest daily fluctuations experienced the greatest decline in renal function by the end of the harvest season.[6] In this study, we present and assess the plausibility of 3 hypotheses as to why these workers experienced severe daily changes in creatinine across the workshift: (i) intense work performed in hot environments with inadequate hydration leads to volume depletion and pre-renal kidney injury[7]; (ii) muscle breakdown throughout the course of the workday leads to transient artificial spikes in serum creatinine[8,9] and/or causes direct renal injury[S1,S2]; and (iii) workers have pre-existing subclinical renal dysfunction that is exacerbated by either volume depletion, muscle breakdown, or a combination of these conditions.[S3] Methods to address these questions are provided in the Supplementary Methods.

RESULTS

There were 103 workers previously classified based on daily changes in creatinine over 6 workshifts.[6] Of these, 89 were present on both day 1 and day 6, resulting in the current analysis study population. A summary of participant demographics and baseline measurements is presented in Table 1.

Volume Depletion

Two groups of workers were identified based on measures of volume depletion, with 5 workers (6%) with similar profiles suggesting volume depletion. The 5 workers identified in this group displayed, on average, higher values for urine specific gravity pre-shift with marked increases post-shift, tended to have a greater loss in body weight from pre- to post-shift, and exhibited higher levels of serum copeptin, a surrogate marker for vasopressin. Individuals with aciduria (defined as a urinary dipstick pH of 5.0) were more likely to be assigned to the non−volume depletion group. There were no discernible differences in serum bicarbonate levels between the groups (Figure 1, Supplementary Table S1).

All 5 volume-depleted workers (100%) were in the severe daily creatinine change subpopulation identified in the previous study,[6] suggesting that 22% of 23 workers experiencing severe cross-shift fluctuations in creatinine also experience volume depletion.

Muscle Breakdown

Measures for day 1 and day 6 are presented in Supplementary Table S2. We observed a negative association between post-shift serum creatine kinase (CK) values and cross-shift change in creatinine ($P = 0.013$).

Table 1. Baseline characteristics of male sugarcane cutters during the 2017–2018 harvest season (N = 89)

	All study participants (N = 89)	Group 1 (n = 84)	Group 2 (n = 5)
Age, yr	29 (7)	29 (7)	34 (13)
Mild hypertension[a], mm Hg	22 (28%)	21 (27%)	1 (33%)
HbA1c, %	5.35 (0.32)	5.33 (0.32)	5.64 (0.27)
NGAL, ng/ml	6.98 (7.16)	7.20 (7.28)	2.81 (0.94)
Cystatin C, mg/l	0.75 (0.27)	0.77 (0.27)	0.50 (0.07)
Serum creatinine, mg/dl	0.87 (0.16)	0.86 (0.15)	1.06 (0.23)
$eGFR_{creatinine}$, ml/min per 1.73 m^2	116 (15)	117 (14)	96 (19)
$eGFR_{cystatin\ C}$, ml/min per 1.73m^2	122 (34)	121 (34)	150 (5)
$eGFR_{combined}$, ml/min per 1.73 m^2	121 (23)	120 (23)	127 (15)
Urine specific gravity	1.012 (0.009)	1.012 (0.009)	1.003 (0.002)
Weight, kg	59.01 (6.36)	58.85 (6.47)	61.96 (2.82)
Blood bicarbonate	28.39 (2.90)	28.45 (2.90)	27.23 (2.93)
Serum copeptin, pmol/l	3.29 (2.67)	3.03 (1.33)	8.33 (10.46)
Urine pH[b]	22 (27%)	22 (29%)	0 (0%)

All measurements were taken at the start of the harvest in November 2017. Presented as n (%) or mean (SD). eGFR, estimated glomerular filtration rate.
[a]Systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥80 mm Hg.
[b]Percentage with urinary dipstick pH = 5.0.

There was no association between CK and post-shift cystatin C ($P = 0.562$) or uric acid ($P = 0.494$). The CK values showed no association with either post-shift hematuria or proteinuria ($P = 0.954$ and $P = 0.846$, respectively).

Pre-season Reduced Kidney Function

Five workers (6%) started the study with a combined estimated glomerular filtration rate ($eGFR_{combined}$) <90 ml/min per 1.73 m^2. Two of these workers (40%) were previously identified in the severe daily creatinine change subpopulation but were not identified in the volume depletion cluster. Baseline characteristics and markers of kidney function are presented in Supplemental Table S3.

DISCUSSION

This exploratory analysis suggests that there is no single, overriding mechanistic pathway that drives the extreme daily cross-shift changes in creatinine seen in the subset of sugarcane harvesters who go on to experience long-term declines in kidney function. The 3 hypothesized mechanisms explained only 30% of the cases of severe daily change in creatinine. This points to a need to research causes in addition to volume depletion, muscle breakdown, and pre-existing reduced kidney function. In addition to these pathways, other personal, work, or environmental factors may be contributing to severe daily creatinine changes.

Substantial evidence suggests that CKDu is associated with conducting intense work in hot environments and that recurrent acute kidney injury ultimately increases the risk of developing CKDu.[7] Although the number of affected individuals in our cohort is small, the data suggest that approximately 22% of the observed severe daily creatinine changes can be attributed to volume depletion. Remarkably, all workers with indicators of volume depletion were classified as having severe daily creatinine changes across the workshift.

Notably, all 5 individuals identified in the volume depletion group had the highest levels of serum copeptin. Vasopressin is released from the posterior pituitary because of the effects of hyperosmolality in the setting of volume depletion and response to heat exposure, and has been suggested as potential mediator of kidney damage.[5] Indeed, in a different study among Guatemalan sugarcane harvesters, we observed that elevated levels of serum copeptin were associated with increases in creatinine and that improvements in hydration among these workers reduced copeptin concentrations, which, in turn, were associated with improvements in kidney function.[S4] The role of vasopressin in the development of CKDu warrants further research.

Interestingly, we found no role of muscle breakdown in the observed severe changes in creatinine across the workshift in our sample. One of the past criticisms of examining daily changes in creatinine in people working at high exertion levels is its potential association with elevated serum CK.[8] In this study, we observed, contrary to hypothesized relationships between muscle breakdown and elevations in serum creatinine, that individuals with the greatest cross-shift change in creatinine had the lowest observed levels of serum CK post-shift. Furthermore, we observed no association between serum CK and cystatin C or uric acid at the end of the workshift. More targeted studies exploring this potential pathway, including the contribution of uric acid release to low-grade kidney

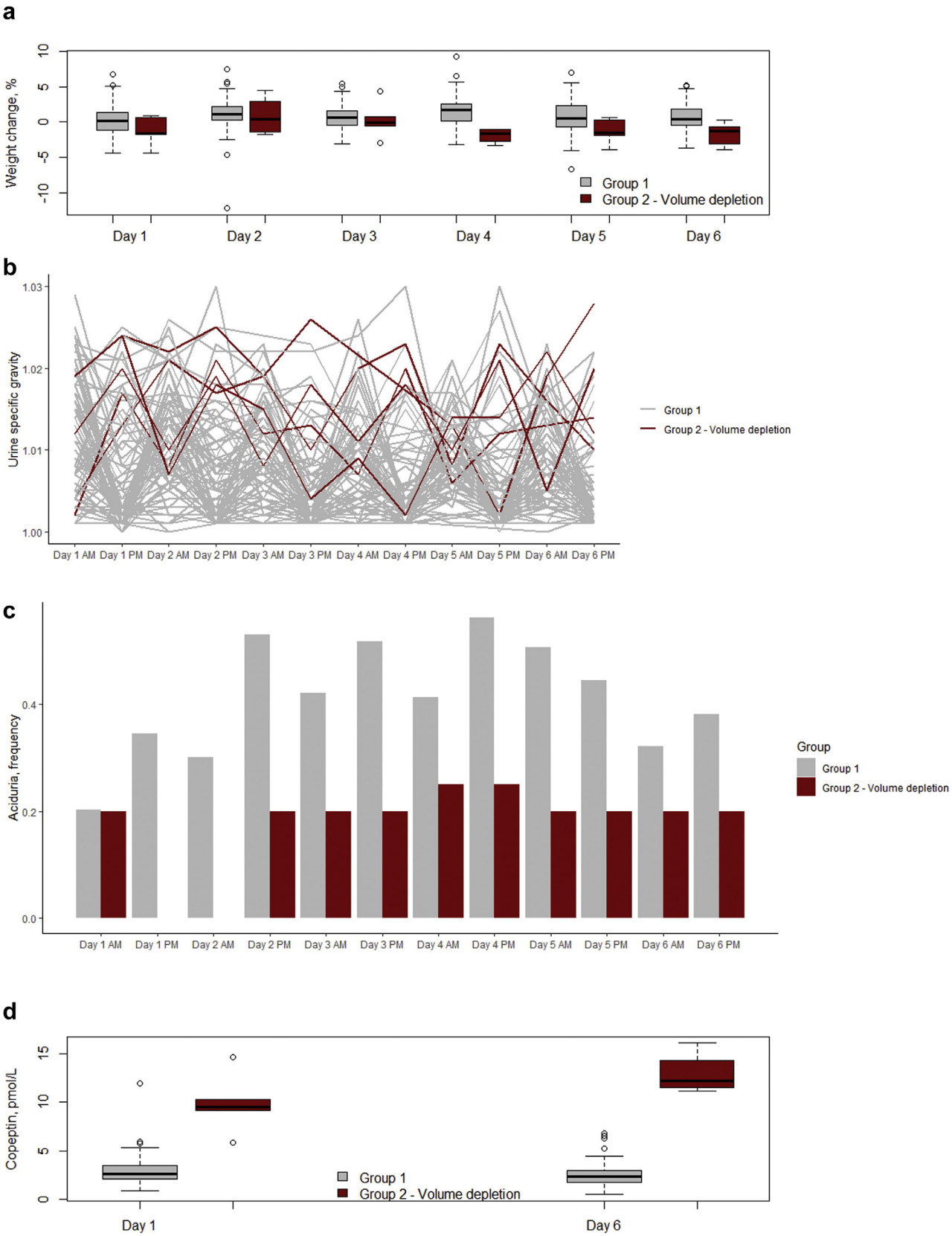

Figure 1. (a) Boxplot of daily weight change. (b) Pre-shift to post-shift changes in urine specific gravity. (c) Frequency of workers with aciduria (urinary dipstick pH of 5.0) at pre- and post-shift. (d) Post-shift measures of copeptin. All figures stratified by groupings resulting from the multivariate mixture generalized linear mixed model based on markers of volume depletion.

injury, are warranted. Lagged effects should be considered, as well.

This study has several limitations. Given our sample size, the study should be considered exploratory. In addition, there is potential for misclassification, first with the previously identified subpopulations as well as with the volume depletion groups. Inclusion criteria required only that workers be present on day 1 and day 6, allowing for the possibility that workers may have not been present in between. Longitudinal data gaps may have affected the cluster assignments. The timing of our sampling may have limited our ability to determine a relationship between serum CK levels post-shift and daily creatinine changes. Changes in meat consumption can affect creatinine and urine pH measures; however, this is unlikely in Guatemala, where workers consume fairly uniform diets low in animal protein.[S5,S6] The timing of the hydration measurements may result in misclassification if some workers drink most of their daily water at the end of the shift. A correction factor for body weight at the end of the day was applied to adjust for the weight of wet clothing, which may overestimate weight loss for some individuals.

In conclusion, this study suggests that severe acute changes in creatinine experienced by sugarcane workers laboring in hot environments over the workday are likely multifactorial. Lines of evidence that warrant further examination include volume depletion, the role of vasopressin in the development of CKDu, and targeted field studies assessing the relationship between elevated CK levels and cross-shift changes in serum creatinine.

DISCLOSURE

All the authors declared no competing interests. University of Colorado has a Memorandum of Understanding with Pantaleon. University of Colorado employed appropriate research methods in keeping with academic freedom, based conclusions on critical analysis of the evidence and reported findings fully and objectively. The terms of this arrangement have been reviewed and approved by the University of Colorado in accordance with its conflict of interest policies.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods

Supplementary References

Table S1.

Table S2.

Table S3.

Table S4.

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