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Association of copeptin, a surrogate marker of arginine vasopressin, with decreased kidney function in sugarcane workers in Guatemala

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Abstract

Background: Vasopressin is elevated in response to heat and dehydration and has been postulated to have a role in the chronic kidney disease of unknown origin (CKDu) being observed in Central America. The aims of this study were to examine whether the vasopressin pathway, as measured by copeptin, is associated with the presence of kidney dysfunction, and to examine whether higher fluid intake is associated with lower circulating copeptin and thereby preserves kidney health among sugarcane workers exposed to hot conditions.

Methods: Utilizing a longitudinal study of 105 workers in Guatemala, we examined relationships between hydration indices, plasma copeptin concentrations, and kidney function markers at three

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times during the 6-month harvest. We also examined whether baseline copeptin concentrations increased the odds of developing an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2.

Results: Copeptin concentrations were positively associated with serum creatinine (β: 1.41, 95% CI: 0.88, 2.03) and negatively associated with eGFR (β: −1.07, 95% CI: −1.43, −0.70). In addition, as workers improved their hydration (measured by increases in fluid balance), copeptin concentrations were reduced, and this reduction was associated with an improvement in kidney function.

Conclusions: Results suggest that copeptin should be studied as a potential prognostic biomarker.

Keywords

Vasopressin; kidney; hydration; agricultural workers

I. Introduction

A high prevalence of chronic kidney disease of unknown origin (CKDu) has been observed among agricultural populations in the Americas and Asia [1]. The pathophysiology of CKDu is unknown. However, agricultural workers perform intense physical work in high ambient temperatures and humidity, which can result in dehydration and potentially produce stress on the kidney [2]. This has led to the hypothesis that chronic exposure to heat stress with concomitant dehydration may increase individual risk and to the need to investigate underlying mechanisms [3].

One potential candidate for inducing renal injury by heat stress is vasopressin. While vasopressin can help the host through urinary concentration, recurrent and chronically elevated vasopressin has been shown to produce experimental renal injury, in part by inducing oxidative stress as well as activation of the polyol pathway [4]. Because vasopressin is unstable with a short half-life, copeptin, a stable component of pre-pro-vasopressin and marker of circulating vasopressin, has emerged as a surrogate biomarker [5] and may help explain biological response mechanisms induced by dehydration and other vasopressin-related stimuli. For example, higher circulating copeptin levels have been associated with kidney dysfunction in general populations [6] and microalbuminuria [7]. Furthermore, there is increasing experimental evidence that chronic elevations in vasopressin may lead to glomerular and tubular damage [8].

We have performed a longitudinal study among sugarcane workers in southwest Guatemala where we evaluated the relationship of plasma copeptin concentrations to hydration and renal function at several times during a harvest season. Our hypothesis was that vasopressin levels (measured via copeptin) are associated with impaired renal function in a sugarcane worker population. Copeptin may help explain biological response mechanisms induced by dehydration and other vasopressin-related stimuli.

Our first aim was to examine the relationships between repeated measures of plasma copeptin concentrations and markers of kidney function and injury including serum

creatinine, estimated glomerular filtration rate (eGFR), urine neutrophil gelatinase-associated lipocalin (NGAL), and urine albumin-to-creatinine ratio (ACR). Our second aim was to examine the association between increased fluid balance and decreases in copeptin concentrations and, in turn, associations with improvements in kidney function. Our third aim was to evaluate the merits of copeptin as an early stage clinical biomarker in agricultural workers at risk for kidney dysfunction, by testing whether higher copeptin concentrations at study baseline were associated with increased odds of having an eGFR < 60 ml/min/1.73 m^2 at the end of the study.

II. Methods

a. Setting and Participants

This research was conducted in a prospective cohort of male sugarcane field workers in Guatemala in 2016–17. The study is described in detail elsewhere [9, 10]. A schematic of the study timeline is provided in the supplement (S1 Figure). Briefly, survey data, and urine and blood samples were collected at the end of the work shift for 105 workers at three time points in February, March, and April 2017 [9]. All participants provided written consent prior to study enrollment. The study was approved by the Institutional Review Board of the University of Colorado and in Guatemala (Comite de Etica, Facultad de Medicina, Universidad Francisco Marroquin-Hospital Universitario Esperanza).

b. Data Collection and Laboratory Analysis

Details on urine and blood measurements and covariate data collection are in the supplement. Copeptin concentration was measured in plasma-EDTA samples and analyzed using an immunoassay analyzer (Kryptor Compact Plus, Thermo Scientific B.R.A.H.M.S Copeptin proAVP, Hennigsdorf, Germany), with a limit of detection of 0.69 pmol/L.

c. Statistical Analysis

Pearson correlation coefficients were used to assess the relationships between plasma copeptin concentrations and hydration indices. Normality was visually assessed and met by the Central Limit Theorem. We also examined relationships between other potential covariates that may be correlated with copeptin, including creatine kinase and tons of cane cut per day [11], electrolyte solution intake [12], and sugar-sweetened beverage intake [13].

To evaluate our first aim, whether repeat cross-sectional measures of plasma copeptin concentrations were associated with markers of kidney function and injury, we used linear mixed-effect (LME) models with a random intercept for each study subject, estimating β and 95% confidence intervals (95% CI). We controlled for potential confounders *a priori*, including hemoglobin A1c (HbA1c), age, systolic and diastolic blood pressure, and change in bodyweight (as an indirect measure of fluid retention) [14]. To assess our second aim, whether increased fluid balance was associated with decreases in plasma copeptin concentrations and, in turn, associated with improvements in kidney function, we computed longitudinal variation in hydration indices (urine specific gravity, urine sodium, serum sodium, and serum osmolality), copeptin and eGFR for each subject between two consecutive time points. We then used LME models with a random intercept for each study

subject to examine relationships between change in hydration indices, change in copeptin concentration, and change in eGFR while controlling for age, HbA1c, and systolic and diastolic blood pressure. Finally, to address our third aim, we examined the influence of plasma copeptin at study baseline on the odds of having an eGFR < 60 ml/min/1.73m^2 at the final time point using logistic regression. All analyses were completed in SAS version 9.4 (Cary, NC).

III. Results

There were 105 workers who participated in the study with a participation rate of 97%. Participant demographics and clinical characteristics are displayed in Table 1. Copeptin concentration distributions are shown in the supplement material (S2 Figure). Copeptin concentrations averaged 5.79 ± 6.96 pmol/L in February, 5.28 ± 4.67 in March, and 3.24 ± 1.70 in April.

Hydration indices, work practices, and kidney function markers are described in Table 2. On average, most participants produced urine samples consistent with adequate hydration, supported by their positive weight change across the work shift, low urine specific gravity, and normal serum osmolality. Copeptin concentrations were significantly correlated with all hydration indices, except cross-shift weight change, and with several kidney markers.

a. Aim 1 results

Univariate results examining the relationships between serial measures of plasma copeptin concentrations and markers of kidney function are shown in the supplement (S1 Table). In the multivariable models, copeptin was positively associated with serum creatinine (β: 1.41, 95% CI: 0.88, 2.03) and inversely related to eGFR (β: −1.07, 95% CI: −1.43, −0.70), Table 3. Copeptin was not related to urine NGAL or urine ACR. Of note, HbA1c was inversely associated with eGFR (β: −15.59, 95% CI: −26.40, −4.78).

b. Aim 2 results

We constructed three models to examine whether increased fluid balance was positively associated with decreases in copeptin concentrations and, in turn, improvements in kidney function between two subsequent time points (S2 Table). In our first model, we observed that increases in urine specific gravity, serum osmolality, and serum sodium were all positively associated with an increase in copeptin concentration, with urine specific gravity associated with the largest change in copeptin (β: 2.68; 95% CI: 1.41, 3.94). In the second model, we observed that an increase in copeptin concentration was negatively associated with a decrease in eGFR (β: −1.08; 95% CI: −1.62, −0.54). In our third model, we examined whether change in hydration indices and/or change in copeptin concentration was associated with change in eGFR. We found that change in copeptin concentration was significantly associated with change in eGFR and none of the hydration indices were significant (Models 3a–3d, S2 Table). In the supplementary material, we present a scatter plot that shows changes in urine specific gravity, copeptin, and eGFR in three dimensions (S3 Figure).

c. Aim 3 results

Our third aim was to evaluate whether higher copeptin concentrations at study baseline were associated with increased odds of having a final eGFR < 60 mL/min/1.73 m^2. The odds ratio of having an eGFR < 60 mL/min/1.73 m^2 was 1.14 (95% CI: 1.05, 1.23, p < 0.01) per 1 pmol/L increase of copeptin at study baseline. Five workers had an eGFR <60 ml/min/1.73 m^2 at their last time point (April) and three of these workers had high initial copeptin concentrations (range: 24–39 pmol/L).

IV. Discussion

The primary findings of this study were that 1) a reduction of urine concentration (through higher fluid intake) was associated with a reduced concentration of copeptin, a surrogate marker of vasopressin; and 2) a reduction of copeptin concentration was associated with an improvement in markers of kidney function. Our findings indicate that plasma copeptin concentrations may be predictive of kidney function decline over several months. An additional novel finding is that higher plasma copeptin concentrations were associated with worse kidney function as indicated by serum creatinine and eGFR, at multiple time points.

These findings suggest that plasma copeptin concentration may be an early marker of decreased kidney function occurring in sugarcane workers. Experimental studies suggest vasopressin may have a role in the kidney injury in models of chronic kidney disease and diabetes [15]. Vasopressin may act in part by increasing glomerular hydrostatic pressure, and vasopressin has been shown to increases albumin excretion in humans [16]. Experimental studies of heat stress-induced kidney injury have also provided evidence that exogenous desmopressin can induce further kidney damage [17], while blocking vasopressin action via the V1a and V2 receptors may ameliorate renal injury (4), especially in the setting where the hydration fluids contain sugar-based solutions containing fructose. Potential mechanisms of injury include elevation in oxidative stress and the concurrent over-activation of the intra-renal polyol (aldose reductase-fructokinase) pathway (4). The proposed mechanism for these effects is that vasopressin may increase glomerular pressure, through activation of the polyol pathway and the induction of oxidative stress, leading to tubular and glomerular injury [18].

Our findings suggest that copeptin may prove to be a useful clinical and research tool for determining if workers are at risk for kidney dysfunction. One clinical trial observed that increased water intake resulted in an attenuation of copeptin over 6 weeks [19]. However, studies that have included interventions to modify vasopressin secretion to observe changes in kidney outcomes are very limited. One intervention study in stage 3 CKD patients used coaching to increase water intake and observed reductions in copeptin. However, the increase water intake did not show a significant slowing in the decline of kidney function after one year [20]. The intervention study was conducted in patients with stage 3 CKD and patients were excluded from the study if they drank > 10 cups of fluid a day which is contrary to this current study. Our study participants were drinking on average 13 liters of water per day.

One of the more provocative findings of this study was that the copeptin relationship to eGFR was observed in subjects who were relatively well hydrated. Besides emphasizing the

potential importance of vasopressin in mediating kidney disease, this study also provides insights regarding osmolar versus non-osmolar stimuli for vasopressin in the setting of heat stress. By following workplace protocols that strongly encouraged water and electrolyte consumption, some individuals developed mild, asymptomatic hyponatremia and positive weight change across the work shift. The observation that mild hyponatremia developed may indicate that copeptin levels may be higher than expected for the given water intake. Vasopressin can be stimulated by a number of other factors among agricultural workers, including extracellular volume depletion [21] and non-osmolar stimuli (i.e., increased body core temperature, physical exercise, and consumption of fructose in rehydration beverages) (4, 11–13). However, the relationship of urine sodium concentration with copeptin concentration was opposite of what was expected (as extracellular volume depletion is associated with a low urine sodium concentration and, in this study, copeptin concentration increased with increasing urine sodium concentration). While we observed a negative correlation between electrolyte fluid and copeptin, we did not observe any relationship between intake of sugar-sweetened beverages and copeptin. These beverages have less salt and potassium than electrolyte fluid which could result in less water retention [22] and, thus, result in less attenuation of copeptin. In contrast, a recent study observed greater increases in serum copeptin in healthy adults (n=12) who only drank soft drinks during and after four hours of exercise in the heat compared to adults who only drank water [23]. The authors suggest the potential role of vasopressin, uric acid, and the polyol-fructokinase pathway in the development of acute kidney injury when drinking soft drinks and exercising in the heat. We included survey questions regarding consumption of energy drinks, juice, and soda in our study, whereas the soft drink study had the participants only drink Mountain Dew® (Mountain Dew, PepsiCo, Purchase, NY) which has higher fructose contents compared to other sugar-sweetened drinks.

Another interesting result that will warrant further study in populations at risk of CKDu was that HbA1c was strongly associated with declines in eGFR. Hyperglycemia and diabetes mellitus are risk factors for kidney dysfunction. However, because of the high prevalence of anemia in Guatemala [24] and because anemia can confound the clinical interpretation of HbA1c [25], we speculate that HbA1c may, alternatively, imply a relationship between anemia and eGFR in our population.

A strength of this study was that it followed a group of workers, sampled three times over 3-months. Despite the inherent challenges of conducting field research under extreme field conditions, the study participation rate was high, and we were able to obtain, transport, and analyze specimens with a high degree of reliability.

There are several study limitations that should be noted. We used plasma copeptin concentration as a surrogate for vasopressin secretion. While a number of studies have validated copeptin as a reliable measure for vasopressin [5], one study found a significant correlation between copeptin and vasopressin levels but copeptin explained only half of the variance of vasopressin [26]. Authors suggest that there is a sharper decrease in the clearance rate of copeptin than vasopressin when GFR decreases. We do not know if the changes in renal function associated with copeptin represent acute, subacute or chronic changes. We relied on creatinine and eGFR to assess short-term kidney function changes and

not actual measured GFR. Actual GFR changes may be even more pronounced than suggested by eGFR changes. There is also the possibility that associations between copeptin and markers of kidney function are unrelated to the pathogenesis of disease. Copeptin may be a functional marker of kidney injury or copeptin may be demonstrating a hemodilution effect which might be the reason it correlates with eGFR. Nevertheless, the experimental studies showing that chronic vasopressin effects can induce renal damage [4] support the relationship of higher copeptin with reduced eGFR. Serum creatinine was measured separately for each time point which may lead to anomalous creatinine estimates. For Aim 3, since only five participants had an eGFR <60 ml/min/1.73 m^2, we were not able to run a multivariable model as this would result in overfitting the models. Finally, we relied on self-reported fluid intake. To mitigate the risk of recall bias, we asked participants to recall that day's fluid intake at the end of the work shift.

In summary, our study provides preliminary evidence that copeptin may be an early marker of kidney dysfunction in agricultural workers at high risk for heat stress. Potential clinical and workplace interventions that mitigate this form of injury should be examined in the face of increasing heat extremes. Further research is warranted to understand the contribution of vasopressin to renal injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Characteristics of study participants, N=105.

Characteristics	Mean (SD)
Age (years)	30 (9)
Job, n (%)	
- Cane cutter	83 (79%)
- Cane seeder	22 (21%)
Body Mass Index (kg/m^2)	23.48 (2.58)
Systolic BP (mmHg)	112 (10)
Diastolic BP (mmHg)	70 (9)
Hypertension [a], n (%)	4 (4%)
Blood glucose (mg/dL)	81.79 (13.69)
HbA1c	5.66% (0.29)
- Diabetic, > 6.5%, n (%)	0 (0%)
Pre-employment eGFR [b] (mL/min/1.73 m^2)	111.11 (15.60)

[a]Defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥90 mmHg.

[b]eGFR (estimated glomerular filtration rate) measured prior to the start of the 6-month harvest.

Table 2:

Descriptive data of biomarkers, work practices, and kidney function, averaged from all time points and their correlations with copeptin.

			Plasma Copeptin	
Characteristics	**N**	**Mean (SD)**	**r**	**p-value**
Change in Bodyweight	265	0.29 (3.18)	−0.08	0.23
Urine Specific Gravity	265	1.005 (0.007)	0.58	**<0.01**
- > 1.020, n (%)	265	24 (9%)		
Serum Osmolality, mmol/kg	264	280.07 (7.78)	0.40	**<0.01**
Serum Sodium, mmol/L	265	135.22 (3.63)	0.26	**<0.01**
Urine Sodium, mEq/L	252	23.56 (26.01)	0.38	**<0.01**
Creatine Kinase, U/L	264	403.80 (291.76)	−0.01	0.82
Cane cut during shift, tons	202[a]	6.12 (2.26)	−0.09	0.21
Water, liters	263	13.27 (5.33)	−0.33	**<0.01**
Electrolyte fluid, liters [b]	260	2.50 (1.50)	−0.32	**<0.01**
Number of sugar-sweetened beverages	257	0.45 (0.93)	0.03	0.60
Urine ACR, mg/mmol	252	2.58 (4.66)	−0.01	0.86
Urine NGAL, ng/mL	253	9.71 (13.38)	−0.01	0.88
Serum creatinine, μmol/L [c]	265	85.75 (22.10)	0.49	**<0.01**
eGFR, ml/min/1.73 m^2	265	105.73 (21.73)	−0.44	**<0.01**
eGFR Categorized		≥ 60 (n= 251)	< 60 (n=14)	p-value [*]
Copeptin, pmol/L		4.73 (4.49)	12.37 (11.02)	**<0.01**

Abbreviations: ACR: albumin-to-creatinine ratio; NGAL: neutrophil gelatinase-associated lipocalin; eGFR: estimated glomerular filtration rate.

[a] Reduced N since 20% of the participants are seeders and do not cut cane.

[b] Electrolyte fluid was distributed in 500-ml bags.

[c] Conversion factor for creatinine in μmol/L to mg/dL divide by 88.4

[*] p-value based on Wilcoxon rank sums test.

Table 3:

Results from multivariable linear mixed -effect models examining associations between plasma copeptin and kidney function markers.

	Serum Creatinine (n=245)		eGFR (n=245)		Urine NGAL (n=234)		Urine ACR (n=233)	
	Estimate (95% CI)	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Copeptin	1.41 (0.88, 2.03)	**<0.01**	−1.07 (−1.43, −0.70)	**<0.01**	−0.04 (−0.23, 0.15)	0.70	−0.004 (−0.87, 0.86)	0.99
HbA1c	19.28 (6.73, 31.84)	**<0.01**	−15.59 (−26.40, −4.78)	**<0.01**	3.43 (−3.64, 10.50)	0.34	0.64 (−1.63, 2.91)	0.58
Age	0.43 (0.01, 0.84)	**0.04**	−1.13 (−1.46, −0.80)	**<0.01**	0.06 (−0.16, 0.28)	0.60	−0.05 (−0.11, 0.01)	0.08
Systolic BP	0.16 (−0.36, 0.67)	0.56	−0.14 (−0.53, 0.26)	0.50	0.0004 (−0.18, 0.18)	0.99	0.01 (−0.05, 0.08)	0.69
Diastolic BP	−0.04 (−0.78, 0.71)	0.92	−0.12 (−0.66, 0.42)	0.66	−0.21 (−0.45, 0.03)	0.09	−0.10 (−0.20, 0.00)	0.05
Weight change, kg	0.009 (−0.42, 0.44)	0.97	−0.14 (−0.53, 0.26)	0.50	0.29 (0.01, 0.57)	**0.04**	0.02 (−0.12, 0.16)	0.83

Abbreviations: eGFR: estimated glomerular filtration rate; NGAL: neutrophil gelatinase-associated lipocalin; ACR: albumin-to-creatinine ratio; BP: blood pressure.