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Schistosomiasis and hydration status: *Schistosoma haematobium*, but not *Schistosoma mansoni* increases urine specific gravity among rural Tanzanian women

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Abstract

Objectives—Schistosome infections can damage organs important in water homeostasis, especially the kidneys. Urogenital schistosomiasis (caused by *Schistosoma haematobium*) increases protein and blood in urine and intestinal schistosomiasis (caused by *S. mansoni*) affects total body water. However, no data exist on how different schistosome species affect urine specific gravity (USG), a hydration biomarker. Therefore, we assessed the relationship between *S. haematobium*- and *S. mansoni*-infected and uninfected women and USG in rural Tanzania.

Materials and Methods—Surveys were conducted and stool and urine samples were collected among 211 nonpregnant women aged 18–50. *S. haematobium* eggs were detected using the urine filtration method. *S. mansoni* eggs were detected using the Kato Katz method. USG was measured using a refractometer and analyzed as both a continuous and dichotomous variable. Regression (linear/logistic) models were estimated to test the relationship between infection and hydration status.

Results—The prevalence of *S. haematobium* was 5.9% and *S. mansoni* was 5.4% with no co-infections. In regression models, *S. haematobium*-infected women had significantly higher USG (Beta=0.007 g/ml; standard error=0.002; p=0.001) and odds (Odds ratio: 7.76, 95% CI: 1.21–49.5) of elevated USG (>1.020 g/ml) than uninfected women, whereas *S. mansoni*-infected women did not.

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Discussion—*Schistosoma haematobium*, but not *S. mansoni*, infection is associated with higher USG and risk of inadequate hydration. Future work should determine whether findings are attributable to parasite-induced debris in urine or urinary tract pathologies and signs of renal damage. Human and non-human primate studies using USG in schistosome-endemic areas should account for schistosomiasis.

Keywords

Schistosomiasis; hydration; kidney pathology; USG

Introduction

Schistosomiasis is a neglected parasitic infection that has a long history of afflicting humans living in tropical regions (Hibbs, Secor, Van Gerven, & Armelagos, 2011). However, human made ecological changes, most notably the construction of dams, have increased the spread of schistosomiasis (Inhorn & Brown, 1990; Sattenspiel, 2000). It currently affects at least 206 million humans worldwide and can damage central nervous, gastrointestinal, pulmonary, and renal systems, leading to severe pain, morbidity, mortality, and loss of economic productivity (World Health Organization, 2017).

Schistosoma ova are shed in urine (*S. haematobium*) or feces (*S. mansoni*), depending on the species that causes infection (Colley, Bustinduy, Secor, & King, 2014). Long-term schistosome infections can lead to chronic kidney disease by multiple mechanisms, including immunologic damage to the kidney itself and scarring in the urinary tract that results in blockage and build-up of pressure in the kidney (Colley et al., 2014; Hatz et al., 1998; Lehman Jr, Farid, Bassily, & Kent, 1970). These changes are associated with increased risk for bacterial infections and end-stage renal disease (Clark et al., 2016).

The fact that schistosomiasis increases the risk of kidney and urinary tract infections suggests that schistosomiasis may also impair the regulation of body water, i.e. hydration status, particularly among those infected with urinary schistosomiasis (*S. haematobium*) (Nmorsi, Egwunyenga, & Nwokolo, 2005; Wami et al., 2015). Interestingly, hydration and renal parenchyma (the functional tissue in the kidney) may also be affected by intestinal schistosomiasis (*S. mansoni*) infection (De Lorenzo et al., 1997). Specifically, total body water was shown to be elevated among adults with *S. mansoni* infection compared to uninfected controls, indicating water retention (De Lorenzo et al., 1997). Importantly, individuals with *S. mansoni* infection in that study had no visible sign of fluid overload. In addition, *S. mansoni* has been associated with glomerulonephritis, in which the kidney's ability to filter waste and extra fluid is impaired (Andrade, Andrade, & Sadigursky, 1971). When organs with a key role in water homeostasis, like the kidney and gastrointestinal tract, are fighting an infection, hydration status is likely to be affected.

Urinary examinations are common for schistosomiasis, yet the connection to hydration status is not fully understood. The relationships between different schistosome species and hydration status are important because they potentially reveal: 1) pathways to hydration dysregulation, 2) early signs of urinary tract and kidney pathologies, and 3) insight into whether these associations could be due to the site of the schistosome infection (i.e. urinary

tract vs gut). The hallmark symptom of *S. haematobium* is blood in the urine (hematuria), classically interpreted as male puberty or menstruation in females in areas of high endemicity (Colley et al., 2014; Dettwyler, 2013). Protein is also elevated in the urine of those with *S. haematobium* infection (Ochodo et al., 2015). Given the multiple urinary and fluid abnormalities associated with schistosome infections, it is surprising that the comparative effects of these two schistosome species on urine specific gravity (USG), a biomarker of hydration and urine concentration, have not been investigated (Atalabi, Adubi, & Lawal, 2017; Nmorsi et al., 2005; Wami et al., 2015).

Therefore, we sought to fill this gap by testing how infection by *S. haematobium* or *S. mansoni*, i.e., urinary versus intestinal schistosomiasis, affects USG compared to non-infection. Given known effects of schistosome infections (particularly *S. haematobium*) on the kidney, we hypothesized that women with *S. haematobium* would have substantially elevated USG and that women with *S. mansoni* would have higher USG than uninfected women, but lower than women infected with *S. haematobium*.

Materials and Methods

Population and study setting

We used an observational, cross-sectional study design to collect data between June and December 2016. We invited a community-based sample of non-pregnant women between the ages of 18 and 50 years living in 11 rural villages in the Mwanza and Shinyanga Regions of northwest Tanzania near Lake Victoria to participate in the study. Women were participating in a larger survey of villages in the region that sought 10 *S. haematobium*-infected women and 10 schistosome-uninfected women for enrollment into an intensive cohort study. All participants were offered free testing and treatment for schistosome infections. Given the known low rate of egg excretion in adults and particularly in women who have active schistosome infections, we predicted that 5% of women screened in this study would have *S. haematobium* eggs detected in urine (Colombe et al., 2018; Downs et al., 2011). Therefore, we anticipated needing to screen 200 women in order to detect 10 who were excreting *S. haematobium* eggs and could be enrolled into the cohort study.

Ethical approval

This study was approved by the Joint Research Ethics Committee of the Catholic University of Health and Allied Sciences/Bugando Medical Centre in Mwanza (BREC/001/01/2009), the National Institute for Medical Research in Dar es Salaam (NIMR/HQ/R.8a/Vol. IX/I313), and the Weill Cornell Medicine Internal Review Board (IRB# 1108011883). All women provided written informed consent before study participation.

Data collection and specimen analysis

Women participated in a structured private interview that covered a range of topics related to exposures, medications, and sexual history and infection status. Interviews were conducted in Kiswahili in a private setting by a trained study nurse and lasted approximately 20 minutes each. Women also provided urine and stool at the study site for testing of *S.*

haematobium and USG, and *S. mansoni*, respectively. All urine samples were collected between 10 am and 2 pm to control for the influence of time of day on hydration status.

Schistosoma haematobium eggs were detected using the urine filtration method with 10 milliliters of urine (World Health Organization, 2006). *S. mansoni* eggs were detected by preparing five slides for microscopic examination from a single stool sample using the Kato Katz method (Berhe et al., 2004; Katz, Chaves, & Pellegrino, 1972). Slides were examined by trained parasitologists from the National Institute of Medical Research in Mwanza, Tanzania.

To measure hydration status, the dependent variable, we used urine specific gravity (USG). This is considered the most reliable non-invasive hydration biomarker for use in the field (L. Armstrong, 2007). USG provides the density of urine relative to water with a value of 1.000 (g/ml) equivalent to water and generally ranges from 1.000–1.040 with values above 1.020 g/ml used as a well-established cutoff for inadequate hydration, or a hypohydrated state, in men and women (L. E. Armstrong et al., 2012; Popowski et al., 2001). A handheld refractometer (Atago Pen) was used to measure USG in the field within 1 hour of sample collection.

Covariates were selected *a priori* based on their established or plausible association with USG. We adjusted for village fixed effects to control for environmental differences and exposures between women and distances walked to clinics and access to different water sources. Age and schooling were self-reported. Education is associated with higher knowledge about the importance of and access to water. Intensive breastfeeding was measured by the lack of a resumption of menses after childbirth to capture women who have the highest water needs (A. Rosinger, 2015a). Ambient temperature was measured using a laboratory grade outdoor thermometer (Fischer Instruments, Drabech, Germany) at the time of the urine sample, as exposure to hotter temperature can increase water needs and affect hydration status (A. Rosinger, 2015b). Treatment of previous schistosomiasis infection at any point in the past was self-reported. We adjust for this to examine whether residual effects of past infection persist on USG.

Statistical analyses

Statistical analyses were conducted in Stata 15.0 (College Station, TX). Descriptive statistics were presented by infection status. Linear and logistic regression models of continuous USG and elevated USG were built using robust standard errors. They are presented first unadjusted, then adjusted for village fixed effects to tease apart community level differences in exposures, and finally additionally adjusted for individual level covariates, age, education, breastfeeding status, ambient temperature, and past treatment. Variance inflation factor (VIF) was used to assess multi-collinearity on all models to assure that multi-collinearity was not significantly affecting the models ($VIF < 10$). Due to large confidence intervals in the logistic regression models, the “Firth” penalized maximum likelihood estimation method was used and these results are presented (and are more conservative than the non-penalized models) (firthlogit in stata) (Heinze & Schemper, 2002). The modelling results are presented in the form of parameter estimates/coefficients (B) and odds ratios (ORs) for linear and logistic regressions, respectively. To assess model fit, R^2 were used for the linear regression

models and akaike information criteria (AIC) was used for logistic regressions (with lower numbers indicating a better fit). We then graphed the predicted USG by infection status controlling for the range of covariates using marginal standardization (Muller & MacLehose, 2014).

To test the robustness of the results, we used a quasi-experimental method to estimate the average treatment effects (ATE) of *S. haematobium* and *S. mansoni* infection on USG with nearest neighbor matching (StataCorp, 2015). This method which was designed for use on observational data creates “treatment” (infected) and comparison (uninfected) groups that are similar in observable ways, conditional on the full set of covariates described above (Drukker, 2016). We estimate the ATE first with urinary schistosomiasis and separately with intestinal schistosomiasis, while controlling for the other infection type using nearest-neighbor matching based on Mahalanobis distance (teffects nnmatch in Stata), matching to the closest two neighbors so that the infected and uninfected women are similar conditional on the set of covariates included in the regression models. This quasi-experimental method creates matched pairs of infected women and uninfected women with similar propensities of being infected conditional on observed covariates. It then examines differences in outcomes in hydration status between women within these pairs averaged across all pairs.

Results

We enrolled a total of 211 non-pregnant women, of whom 209 provided urine samples, 205 provided fecal samples, and 204 had samples for both urine and feces. One woman had missing covariate data measurement, which yielded a final analytic sample of 203 women with all co-variables. Among the eight women excluded, two had *S. haematobium* infection.

Twelve of the 203 women who provided urine samples tested positive for *S. haematobium* giving a prevalence of 5.9%, while 5.4% tested positive for *S. mansoni*. None of the women were infected with both species of schistosomes. The median urine egg count in women with *S. haematobium* infection was 1.5 per 10 ml (interquartile range [IQR]: 2.5) and the median stool eggs per gram in women with *S. mansoni* infection was 14.4 (IQR: 31.2). Descriptive statistics of the different groups are presented in Table 1.

Unadjusted for covariates, *S. haematobium*-infected women had significantly higher USG (Beta [B] = 0.0039 g/ml, robust standard errors [SE] = 0.0014, $p = 0.003$) and three times the odds (OR: 3.07, 95% confidence interval [CI]: 1.02, 9.21) of elevated USG (>1.020 g/ml) than uninfected women (Model 1, Tables 2 & 3). Adjusting for village fixed effects, the coefficient (B = 0.0065 g/ml, SE = 0.002) and odds (OR: 8.01, 95% CI: 1.32, 48.8) of elevated USG increased substantially (Model 2 in Tables 2 & 3). Controlling for individual-level covariates, the results were stronger still (B = 0.0069 g/ml, SE = 0.002, Model 3, Table 2; OR: 7.76, 95% CI: 1.21, 49.5; Model 3, Table 3).

In contrast, *S. mansoni*-infected women did not have greater USG or odds of elevated USG relative to uninfected women, including in models adjusted for all covariates (B = -0.0008 g/ml, SE = 0.0025, $p = 0.76$; OR: 1.38, 95% CI: 0.40, 4.82; Model 3 in Tables 2 & 3).

Using the results from Model 3 in Table 2, *S. haematobium*-infected women had a predicted USG of 1.0233 g/ml (95% CI: 1.0193, 1.0274), which falls mostly above the cutoff for dehydration, and is significantly higher than uninfected women (USG = 1.0165 g/ml, 95% CI: 1.0155, 1.0174) (Figure 1). *Schistosoma mansoni*-infected women had a predicted USG of 1.0157 g/ml (95% CI: 1.0108, 1.0206).

The robustness analyses provide additional support for the main analyses, as the average treatment effect (ATE) coefficient for urinary schistosomiasis was significantly related to increased USG (B = 0.0045; Abadie-Imbens [AI] Robust SE = 0.0017, p = 0.007, n = 203). Additionally, the ATE coefficient for *S. mansoni* was not significantly related to USG (B = -0.001; AI Robust SE = 0.003; p = 0.74, n = 203).

Discussion

We hypothesized that women with *S. haematobium* would have substantially elevated USG and that women with *S. mansoni* would have higher USG than uninfected women, but lower than women infected with *S. haematobium*. The data from the present study indicated that *S. haematobium*, but not *S. mansoni*, was associated with significantly higher USG as well as higher odds of elevated USG than uninfected women in both unadjusted and adjusted models and robustness analyses (Table 2 & 3; Figure 1). This effect size of 0.006 g/ml represents a total body water loss of ~1–2%, (Popowski et al., 2001) and is of physiologic significance given studies showing that mild dehydration or water loss of 2–3% has been associated with adverse effects including impaired cognition, poorer athletic performance, mood changes, and higher risk of kidney stones (Popkin, D'Anci, & Rosenberg, 2010). On a practical level, this effect size was associated with an average shift above the dehydration cutoff point (1.020 g/ml) as the average USG went from a normal, euhydrated state (1.016 g/ml) to a dehydrated or hypohydrated state (1.023 g/ml). The finding that urinary schistosomiasis is associated with elevated USG is consistent with previous studies which have found that *S. haematobium* infection was associated with elevated USG (>1.020 g/ml) (Nmorsi et al., 2005). Two early case studies indicated that chronic schistosomiasis was associated with impaired renal concentration after 24 hours of water deprivation, but that it was also associated with darker urine, which would indicate a higher concentration (Farid et al., 1967; Girges, 1929).

The finding that USG of women infected with *S. mansoni* was not significantly different than uninfected women ran contrary to our hypothesis. Previous research found that a subclinical increase in total body water was observed among *S. mansoni* infected adults, though USG was not measured (De Lorenzo et al., 1997). Together, these findings may suggest that body water is dysregulated, but it may manifest in changes in intracellular versus extracellular fluid rather than in urine concentration. Our study highlights the importance of accounting for the different species of schistosomes when assessing their impact on hydration status, which to our knowledge has not previously been demonstrated.

The potential pathways through which schistosomiasis affects USG measurements include shedding of schistosome eggs and host bleeding in urine as well as increased stress on the kidneys. Almost all women in our study who had *S. haematobium* infections had light

infections, consistent with previous research demonstrating a typical geometric mean of egg output per 10 mL of urine is only 1–2 eggs for women 20–45 years of age (Colley et al., 2014). It is unclear how much a small output of eggs would increase concentration in measurements of USG. Moreover, schistosomiasis, particularly *S. haematobium*, may also affect hydration through increased stress on the kidneys as the infection may force a tradeoff: filter waste or fight off the infection. This tradeoff may decrease the body's ability to modulate hydration effectively.

The implications of our findings extend to human and non-human primate research related to body water and hormones. Our data supports the recommendation that schistosomiasis should be taken into account when using bioelectric impedance analysis to measure total body water because of water retention among adults infected with *S. mansoni* (De Lorenzo et al., 1997). In addition, humans are not the only primate that suffers from schistosomiasis. Evidence has mounted that various species are both susceptible to and affected by *S. haematobium* and *S. mansoni* (Lovell, 1991; Standley, Mugisha, Dobson, & Stothard, 2012). For example, chimpanzees in both the Ngamba Island Chimpanzee Sanctuary in Uganda and the Sweetwaters Chimpanzee Sanctuary in Kenya tested positive for *S. mansoni* (Standley et al., 2012). Along this same vein, researchers studying sex and stress hormones in urine who adjust for specific gravity may need to account for schistosomiasis as well because the concentration of urine affects the measurements (Anestis, Breakey, Beuerlein, & Bribiescas, 2009). Therefore, both human and non-human primate studies interested in measuring hydration status and hormones using USG in schistosome-endemic areas should account for schistosome infection status.

Limitations

This study is subject to a few limitations. First, the cross-sectional nature of our data means that we cannot attribute causality. Nevertheless, our analytic robustness testing utilized a quasi-experimental method to match infected women to uninfected women similar in observable ways and likely to experience infection given the observed covariates. Results were consistent with the main regression results. Second, this study was limited by a small sample size of infected women; which limited the ability to detect differences between *S. haematobium* and *S. mansoni*. Third, we lack information on other key variables that could confound the relationship between infection status and USG, namely adiposity, water intake, and physical activity as well as the presence of hematuria or proteinuria in our study participants (A. Y. Rosinger, Lawman, Akinbami, & Ogden, 2016). However, despite no anthropometric measurements, prevalence of obesity and overweight are low (~11%) in this region of Tanzania (Mosha et al., 2017) and physical activity and dietary profiles are fairly homogenous. Nevertheless, some residual confounding may remain in the estimates.

Future directions

Future work should determine whether findings are attributable to parasite-induced debris and shedding of eggs in urine or urinary tract pathologies and early signs of renal damage (Colley et al., 2014; Hatz et al., 1998). Longitudinal analysis is needed to track women at different time points in their infection status from uninfected to infected and post-treatment to observe if there is a sequential increase and subsequent decrease in USG similar to

changes in urinary tract pathologies caused by schistosomiasis (Hatz et al., 1998). Relatedly, future work should examine whether *S. haematobium* and *S. mansoni* infections are associated with changes in plasma osmolality, a blood biomarker of hydration status. This examination would further test whether schistosome species affect changes in electrolyte balance and extracellular vs intracellular fluid balance or whether the infections are limited to kidney and urinary tract pathologies.

Overall, our findings indicate that urinary, but not intestinal, schistosomiasis may affect the kidneys and processes of urine concentration and hydration. These findings have relevance to human biology and pathology for both human and non-human primate studies involving urinalysis and provide insight into the progression of chronic kidney disease related to *S. haematobium*. Proper hydration is critical for optimal health, physiological processes, cognitive function, and kidney function (Popkin et al., 2010). Understanding how schistosomiasis potentially disrupts body water homeostasis leading to additional comorbidities, like dehydration, suffered by vulnerable populations deserves more attention.

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Figure 1.

Predicted urine specific gravity and 95% confidence intervals by schistosome infection status adjusted for covariates among Tanzanian women, n=203. Figure is built from Model 3 in Table 2.

Note. Controlling for age, sex, temperature, breastfeeding, village, education. USG > 1.020 is dehydrated state.

Table 1

Characteristics of women infected with *S. mansoni*, with *S. haematobium*¹, and uninfected without missing data (n=203)

	Uninfected women (n=180)	Infected with <i>S. haematobium</i> (urinary) (n=12)	Infected with <i>S. mansoni</i> (intestinal) (n=11)
Age (years), mean (SD)	30.4 (7.9)	24.6 (7.3)	33.0 (7.5)
Education (years), mean (SD)	6.2 (2.8)	5.3 (3.7)	6.0 (2.3)
Past treatment of schistosomiasis, % (SD)	23.9 (42.8)	16.7 (38.9)	9.1 (30.2)
Ambient temperature (degrees °C) ² , mean (SD)	25.8 (3.2)	29.0 (3.4)	25.1 (2.2)
Urine specific gravity (USG) (g/ml), mean (SD)	1.017 (0.006)	1.021 (0.005)	1.016 (0.008)
Dehydrated (USG >1.020 g/ml), % (SD)	27.2 (44.6)	58.3 (51.5)	36.4 (50.5)
Currently breastfeeding without resumption of menstrual cycle, % (SD)	18.9 (39.2)	16.7 (38.9)	9.1 (30.2)

¹No co-infection of *S. haematobium* and *S. mansoni*.

²Ambient temperature taken at time of urine sample.

Linear regressions examining relationship between schistosome species and urine specific gravity¹ among Tanzanian women

Table 2

Independent variables	Model 1 USG (g/ml) Beta	Model 2 USG (g/ml) Beta	Model 3 USG (g/ml) Beta
Infection Status			
No infection	Reference	Reference	Reference
<i>S. haematobium</i>	0.0039** (0.0014)	0.0065** (0.0020)	0.0069** (0.0021)
<i>S. mansoni</i>	-0.0006 (0.0025)	-0.0012 (0.0025)	-0.0008 (0.0025)
Age (years)			-0.0000 (0.0001)
Education (years)			0.0002 ⁺ (0.0001)
Past treatment of Schistosomiasis			0.0006 (0.0011)
Intensive breastfeeding ²			0.0016 (0.0011)
Temperature °C			0.0003 (0.0004)
Village fixed effects ³	no	yes	yes
Observations ⁴	204	204	203
R-squared	0.02	0.08	0.11

Robust standard errors and 95% confidence intervals in parentheses

** p<0.01,

* p<0.05,

⁺ p<0.1

¹ Models include constants, but not displayed.

² Currently breastfeeding without resumption of menstrual cycle.

³ Village fixed effects (n - 1 = 10).

⁴ Observations vary due to 1 missing value for covariates.

Table 3

Logistic regressions (using Firth Method) examining relationship between schistosome species and odds of elevated USG^{1,2} among Tanzanian women

Independent variables	Model 1 ¹ Elevated USG OR (95% CI)	Model 2 ¹ Elevated USG OR (95% CI)	Model 3 ¹ Elevated USG OR (95% CI)
Infection Status			
No infection	1	1	1
<i>S. haematobium</i>	3.07 [*] (1.02 – 9.21)	8.01 [*] (1.32 – 48.8)	7.76 [*] (1.21 – 49.5)
<i>S. mansoni</i>	1.59 (0.47 – 5.36)	1.29 (0.37 – 4.46)	1.38 (0.40 – 4.82)
Age (years)			0.99 (0.95 – 1.03)
Education (years)			1.04 (0.92 – 1.16)
Past treatment of Schistosomiasis			1.18 (0.56 – 2.48)
Intensive breastfeeding ³			1.16 (0.52 – 2.57)
Temperature C			1.07 (0.83 – 1.37)
Village fixed effects ⁴	no	yes	yes
Observations ⁵	204	204	203
AIC	243.4	246.3	233.0

Robust standard errors and 95% confidence intervals in parentheses

^{**}
p<0.01,

^{*}
p<0.05,

⁺
p<0.1

¹
Elevated USG >1.020 g/ml.

²
Models include constants, but not displayed.

³
Currently breastfeeding without resumption of menstrual cycle.

⁴
Village fixed effects (n – 1 =10).

⁵
Observations vary due to 1 missing value for covariates.