PRO-INFLAMMATORY CYTOKINES AND C-REACTIVE PROTEIN ARE ASSOCIATED WITH UNDERNUTRITION IN THE CONTEXT OF SCHISTOSOMA JAPONICUM INFECTION

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Abstract. Schistosomiasis is associated with undernutrition, but the mechanisms involved remain unknown. We analyzed baseline and follow-up data from a longitudinal treatment–reinfection study in N = 477 Schistosoma japonicum–infected subjects 7–20 years of age from Leyte, the Philippines. After baseline treatment with praziquantel, follow-up visits were scheduled every 3 months for 18 months; stool, venous blood, and anthropometric measurements were collected at each visit. Cytokine production by peripheral blood mononuclear cells (PBMCs) stimulated with specific S. japonicum antigens was measured once 4 weeks after treatment. After adjustment for confounders, S. japonicum intensity was associated with decreased serum albumin and Z-scores (all P < 0.01) and with increased serum C-reactive protein (CRP) and interleukin (IL)-6. CRP was associated with decreased albumin and Z-scores (all P < 0.01). Production of IL-1b and tumor necrosis factor (TNF-α) in response to worm antigen was associated with decreased albumin (both P < 0.005) and height-for-age Z-score (TNF-α only, P = 0.05). S. japonicum–associated undernutrition may, in part, result directly from inflammation.

INTRODUCTION

Chronic schistosomiasis affects > 200 million people in 77 countries,1 the majority of whom are infected at low intensity. Schistosoma japonicum infects ~2.4 million individuals, and 70 million are at risk of infection, mainly in China and Southeast Asia.2 Children are affected at highest prevalence and intensity.1 Several studies have shown a relationship between chronic schistosomiasis japonica and undernutrition,3–5 but the mechanisms mediating this relationship have not been elucidated.

The pro-inflammatory cytokines tumor necrosis factor α (TNF-α), interleukin (IL)-1b, and IL-6 have been implicated as mediators of undernutrition and cachexia in a wide variety of chronic diseases.6,7 These cytokines can affect nutritional status through induction of anorexia or appetite suppression8 and through direct metabolic changes such as induction of an increased catabolic state.6 Furthermore, they regulate the acute phase response, which has detrimental effects if persistent6; continuous hepatic production of acute phase proteins, such as C-reactive protein (CRP), results in reprioritization of essential amino acids away from skeletal muscle, the main source of protein within the body.6,9

Knowledge of the role of pro-inflammatory cytokines in schistosomiasis mainly stems from efforts to elucidate the immunologic mechanisms of hepatic fibrosis and hepatosplenic disease. IL-6 and TNF-α are thought to play a role in granuloma formation.10,11 In vitro stimulation of peripheral blood mononuclear cells (PBMCs) with specific schistosome antigens resulted in significantly greater TNF-α production in S. mansoni–infected hepatosplenic subjects compared with non-hepatosplenic, infected controls.10 In addition, spontaneous PBMC production of IL-6 and TNF-α was greater in S. mansoni–infected individuals than in uninfected controls.12 Elevated serum levels of IL-6, TNF-α, and soluble TNF receptor I (sTNF-RI) have been associated with S. mansoni in animals and humans and were higher in acute than in chronic disease.10,11,13–15 Although they lack the antigenic specificity of stimulated PBMC cultures, cytokine levels measured in serum may be more proximate mediators of undernutrition, because they more closely reflect the cytokine environment experienced by the relevant target tissues and organs.

The objective of our analyses was to evaluate whether chronic S. japonicum infection and reinfection after treatment with praziquantel were associated with 1) nutritional status and 2) serum cytokines (IL-1b, IL-6, TNF-α, and sTNF-RI) and CRP, and 3) whether these cytokines and CRP, as well as pro-inflammatory cytokines produced by PBMCs in response to specific schistosome antigens, were associated with decreased nutritional status. Establishment of these relationships would suggest a role for proinflammatory immune responses in the pathogenesis of S. japonicum–associated undernutrition.

MATERIALS AND METHODS

Study site and population. This prospective longitudinal treatment–reinfection study was conducted in three S. japonicum–endemic rice-farming villages in Leyte, the Philippines. In total, 77.6% (N = 982/1,265) of individuals 7–20 years of age residing in the three study villages were screened for the presence of S. japonicum infection by duplicate examination of three stool samples before enrollment. The prevalence of infection with S. japonicum in this age range was 61.6%. Subjects were eligible if they were infected with S. japonicum, lived primarily in a study village, were between 7 and 20 years

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of age, were not pregnant or lactating, and had no chronic disease, severe wasting (defined as body mass index [BMI] less than the third percentile of a reference population of same age and sex derived from the US National Health & Anthropometric Examination Survey), or severe anemia (hemoglobin < 7 g/dL), and provided both child assent and parental consent or adult consent if > 18 years old. Participants were enrolled during two periods: October 2002 and April 2003. Although the main study, designed to investigate immune correlates of resistance to *S. japonicum* reinfection, enrolled subjects 7–30 years of age, this paper is limited to subjects 7–20 years of age, because 1) height-for-age Z-score (HAZ) and BMI are only calculable up to age 20 and 2) subjects in this age range are still growing and represent a more homogeneous study population. At the start of the study (baseline), all *N* = 477 participants were treated with praziquantel (60 mg/kg in a split dose). Stool, anthropometric data, and peripheral blood samples were collected at baseline and at 1, 3, 6, 9, 12, 15, and 18 months after treatment. PBMCs and data on socio-economic status (SES) were collected once. Participants who did not come to the study laboratory at any time-point after baseline and missed all subsequent follow-up visits were considered lost to follow-up. The study was approved by the Institutional Review Boards of Brown University and The Philippines Research Institute of Tropical Medicine. All *S. japonicum*–reinfected and geohelminth-infected subjects were treated at the end of the study.

**Stool examination.** Parasite egg counts were determined at each time-point by duplicate examination of three consecutive stool specimens obtained from each study participant. Each stool specimen was evaluated for *S. japonicum, Ascaris lumbricoides, Trichuris trichuria,* and hookworm egg counts by the Kato Katz method. For each of the stool specimens, the average number of eggs per gram (epg) of the duplicate test was determined; the overall mean number of epg was derived by averaging the egg count of the three individual specimens. Reinfection was defined as having *S. japonicum* eggs in the stool after treatment. In total, 19.3% of available stool results at follow-up were intermittently negative, although the individual was reinfected at a previous follow-up. These results were considered to be false negative (falling below detection level); these egg counts were imputed using the “last value carried over” method. Low, moderate, and high *S. japonicum* intensity infection was defined as 1–99, 100–399, and ≥ 400 epg, respectively. Duration of reinfec-

**Nutritional assessment.** At each time-point, participants were measured while wearing light clothing and no shoes and were weighed to the nearest 0.1 kg on a Seca Model 880 Digital scale (Hanover, MD). Height was measured to the nearest 0.1 cm with a portable anthropometer. These measurements were used to determine the height-for-age Z-score (HAZ), BMI (weight/height²), and BMI Z-score (BMIZ). The Centers for Disease Control (CDC) reference curves (2000) were used to calculate these Z-scores by use of EpiInfo software (version 2000). BMIZ is the index of choice for the assessment of recent undernutrition in adolescents. HAZ represents long-term growth and nutritional status.**

Using a non-stretch “Zerfuss” insertion tape (Ross, USA). Triceps and subscapular skinfolds were measured as described. Upper arm muscle area (cm²) was calculated based on triceps skinfold and MUAC. Age- and sex-specific sum of subscapular and triceps skinfold Z-scores (SSFZ) and upper-arm muscle area Z-scores (UMAZ) were calculated, using a healthy reference population. SSFZ represents subc-

**Socio-economic status.** A summary SES score based on questionnaire data addressing parental and child educational status, occupational status, ownership of home/land, and assets was calculated for each participant as described.

**PBMC collection, *S. japonicum* antigens, and PBMC cytokines.** Once, at 4 weeks after treatment, venipuncture was performed, and blood was collected into Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ) containing heparin as an anti-coagulant. PBMCs were isolated as described. Soluble egg extract (SEA) was prepared according to standard procedures. Soluble worm antigen preparation (SWAP) was prepared as described previously. PBMCs were stimulated with SWAP, SEA, and control media as described. Culture supernatants were collected and analyzed for cytokine production with a custom multiplexed assay kit as described. Results for PBMC production of IL-1β and TNF-α were included in these analyses.

**Blood collection, processing, and analysis.** At each visit, venipuncture was performed, and blood was collected into Vacutainer tubes without anti-coagulant (Becton Dickinson). Serum cytokines and C-reactive protein (CRP) were analyzed by use of a multiplex bead-based platform (BioRad, Irvine, CA) and custom assay kits as described. Results for cytokines that likely play a role in undernutrition (serum IL-1β, IL-6, TNF-α, and sTNF-RI) were included in these analyses. Albumin was determined with commercial kits (ThermoDMA, Louisville, CO) as described. All pipetting and sample identification was performed by a barcode-enabled, high-speed pipetting robot (Tecan, Research Triangle Park, NC). Hypoalbuminemia was defined as serum albumin < 35 g/L.

**Statistical analyses.** Non-normally distributed variables (all egg counts, CRP, and all cytokines) were log-transformed [ln(n + 1)]. Presented regression estimates (β) are interpreted as mean change of the outcome per log-unit increase of the predictor. Because serum IL-6 was undetectable in a substantial proportion of subjects, it was dichotomized into responders (cytokine detectable; > 1.45 pg/ml) and non-responders (cytokine not detectable).

Analyses were split into two parts to disentangle the effects of chronic infection and reinfection: 1) cross-sectional analyses evaluating pre-treatment associations at baseline and 2) longitudinal analyses evaluating associations 3–18 months after treatment, using measurements recorded every 3 months. Longitudinal analyses of reinfec-

**Results for PBMC production of IL-1β and TNF-α were included in these analyses.**
logistic regression models were fit. For longitudinal analyses of continuous outcomes, repeated measures linear regression models were fit. Per repeated measures model, we assessed the optimal covariance matrix to specify the within-person correlation of observations over time. For longitudinal analyses of dichotomous outcomes, marginal models were fit using generalized estimating equations (GEEs). Estimates and 95% confidence intervals (CIs) are based on empirical SEs.

Models evaluating the relationship between *S. japonicum* and serum cytokines were adjusted for sex, age, and geohelminth egg counts. Models of *S. japonicum* and nutritional status were additionally adjusted for SES. Models of serum cytokines and nutritional status were adjusted for sex and age. Separate inclusion of geohelminth egg counts was evaluated in these models but did not alter the regression coefficient of interest >10% or improve model fit, and thus were not included in the final models. Models evaluating the relationship between PBMC cytokines and nutritional status were adjusted for unstimulated, i.e. constitutive cytokine production, sex, and age.

### RESULTS

#### Descriptive characteristics

Table 1 presents study characteristics at baseline. *N* = 449/477 (94.1%) individuals were cured after treatment. At final follow-up 18 months after treatment, *N* = 339 of 382 individuals who provided a stool sample (88.7%) were reinfected; of these, *N* = 262 had a low-intensity reinfection and *N* = 77 had a moderate or high-intensity reinfection. Of the 477 subjects present at baseline, 71 (14.9%) were lost to follow-up by the end of the study. Compared with those not lost to follow-up, they were significantly older, more likely to be women, had lower baseline *S. japonicum* egg counts, and had better BMIZ and UMAZ at baseline. After adjusting for age and sex, the latter three differences were no longer significant (data not shown).

**S. japonicum and nutritional status.** Baseline *S. japonicum* egg count was inversely associated with HAZ (β, −0.07; *P* = 0.01), UMAZ (β, −0.05; *P* = 0.03), and albumin (β, −0.48; *P* = 0.008). High-intensity infection at baseline was associated with 0.34 lower mean BMIZ, 0.21 lower mean UMAZ, and 2.6 g/L lower mean serum albumin compared with low- and moderate-intensity infection combined (*P* = 0.009, 0.017, and 0.018, respectively). In addition, high- compared with low-intensity infection was associated with hyperalbuminemia (odds ratio [OR], 2.72; 95% CI, 1.01−7.32; *P* = 0.047). Prevalence of hypoalbuminemia declined from 10.4% at baseline to 6.5% and 1.4% at 3 and 6 months after treatment, respectively, and remained this low until final follow-up.

In longitudinal analyses, follow-up *S. japonicum* egg count was inversely associated with albumin (β, −0.18; *P* < 0.0001) but not with Z-scores. Duration of reinfection was inversely associated with BMIZ (β, −0.01; *P* = 0.05) and albumin (β, −0.06; *P* = 0.002).

No association was found between SSFZ and baseline or follow-up *S. japonicum* egg count (data not shown).

Because albumin has been described as a negative inflammatory marker, models of albumin were adjusted for CRP in addition to other confounders. Importantly, *S. japonicum* remained a significant negative predictor of serum albumin, although for the relationship between follow-up egg count and albumin, the estimate was attenuated by 27% (data not shown).

**S. japonicum and serum cytokines.** We evaluated whether baseline and follow-up *S. japonicum* intensity was associated with serum levels of CRP and pro-inflammatory cytokines (IL-1b, IL-6, TNF-α, and sTNF-RI). Baseline *S. japonicum* egg count was positively associated with CRP (β, 0.19; *P* < 0.0001). Follow-up egg count was positively associated with both CRP (β, 0.08; *P* < 0.0001) and detectable IL-6 (β, 0.27; *P* < 0.0001). Figure 1 shows levels of CRP and adjusted prevalences of IL-6 responders across categories of *S. japonicum* intensity at baseline (Figure 1A) and follow-up (Figure 1B).

No significant associations were found between baseline or follow-up *S. japonicum* intensity and serum IL-1b, TNF-α, or sTNF-RI (data not shown).

**Serum cytokines and nutritional status.** We evaluated whether CRP and IL-6, both positively associated with *S. japonicum*, were associated with decreased Z-scores and serum albumin. Regression coefficients for the different relationships are presented in Table 2. In both cross-sectional (baseline) and longitudinal (follow-up) analyses, CRP showed a negative association with BMIZ and UMAZ (Figure 2). In addition, CRP was negatively associated with albumin longitudinally (*P* < 0.0001) and showed a near-significant negative association with HAZ at baseline (*P* = 0.06). IL-6 responders showed a trend of decreased UMAZ at baseline (*P* = 0.06).

**S. japonicum-specific cytokines and nutritional status.** Because serum cytokines are not necessarily specific for *S. japonicum*, we also evaluated the cross-sectional relationship between cytokine production in response to SWAP and SEA.
and nutritional status at 4 weeks after treatment. IL-1b to SWAP showed a negative association with albumin, and TNF-α to SWAP was negatively associated with both HAZ and albumin (Table 3).

**Table 2**

Cross-sectional and longitudinal associations between both CRP and IL-6 and nutritional status

<table>
<thead>
<tr>
<th></th>
<th>HAZ</th>
<th>BMIZ</th>
<th>UMAZ</th>
<th>Albumin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ln CRP (µg/mL)†</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>-0.09 (P = 0.057)</td>
<td>-0.16 (P = 0.0006)</td>
<td>-0.16 (P &lt; 0.0001)</td>
<td>-0.27 (P = 0.33)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>0.00 (P = 0.59)</td>
<td>-0.08 (P &lt; 0.0001)</td>
<td>-0.03 (P = 0.008)</td>
<td>-0.57 (P &lt; 0.0001)</td>
</tr>
<tr>
<td><strong>IL-6 responders‡</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>-0.06 (P = 0.52)</td>
<td>-0.09 (P = 0.32)</td>
<td>-0.14 (P = 0.061)</td>
<td>0.90 (P = 0.14)</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>-0.00 (P = 0.90)</td>
<td>-0.04 (P = 0.10)</td>
<td>-0.01 (P = 0.79)</td>
<td>-0.44 (P = 0.17)</td>
</tr>
</tbody>
</table>

†All models were adjusted for sex, age, and clustering at the household level using multivariate regression analyses.
‡Estimates represent mean difference per unit change in ln CRP.
§Estimates represent mean difference for IL-6 responders (cytokine level detectable) compared with non-responders (cytokine level not detectable).
HAZ, height-for-age Z-score; BMIZ, body mass index Z-score; UMAZ, upper-arm muscle area Z-score.

**DISCUSSION**

This study describes results from a human population study examining associations between pro-inflammatory cytokines and CRP and undernutrition in the context of *S. japonicum* infection. Our results strongly support the causal relationship between *S. japonicum* infection and undernutrition, independent of potential confounders: SES and geohelminth infections. Additional support for this relationship comes from a previous paper of the same cohort describing nutritional responses to treatment. The use of both cross-sectional and longitudinal data allowed us to examine nutritional parameters that represent chronic undernutrition (HAZ) and nutritional parameters expected to change more rapidly with treatment and subsequent reinfection (albumin, BMIZ, SSFZ, and UMAZ). The inverse relationship between nutritional parameters and 1) serum CRP, which was positively associated with *S. japonicum*, and 2) worm antigen-induced IL-1b and TNF-α, suggest a role of inflammatory mediators in the pathogenesis of *S. japonicum*-associated undernutrition.

Immunologic studies of schistosomiasis-associated morbidity have focused on hepatic fibrosis and hepatosplenic disease. The health impact of subtle morbidity, such as undernutrition, which affects a far larger percentage of individuals with chronic schistosomiasis, has only recently been acknowledged. Pro-inflammatory cytokines can affect nutritional status through two major pathways: 1) they induce anorexia, resulting in decreased nutritional intake and dietary insufficiency, and 2) these cytokines induce direct metabolic changes such as increased resting energy expenditure and increased catabolism, which is related to a persistent acute phase response during chronic inflammation, resulting in a negative energy balance. Because increased caloric intake does not improve cachexia caused by chronic disease,† the impact of dietary supplementation alone may be limited. Conversely, treatment with praziquantel will likely be an appropriate strategy to improve *S. japonicum*-associated undernutrition.

Persistence of the acute phase response caused by chronic inflammation results in increased hepatic protein synthesis and drives the loss of skeletal muscle, the largest pool of essential amino acids within the body. In adult hemodialysis patients, who experience chronic inflammation, CRP was associated with malnutrition and decreased appetite.*** and both serum IL-6 and CRP were negatively associated with muscle mass.*** CRP synthesis is induced mainly by IL-6, and to a lesser degree by IL-1b and TNFα.*** We found no associations between *S. japonicum* and serum IL-1b, TNFα, or...
Although no previous studies of schistosomiasis have evaluated serum albumin as a nutritional parameter, hypoalbuminemia associated with schistosomiasis has been attributed to decreased hepatic synthesis and intestinal malabsorption. In our cohort, hepatic function is unlikely to be abnormal, because, in the absence of severe liver pathology, which was an exclusion criterion in our study, hepatic function remains unaffected during chronic schistosomiasis. Both inflammation and inadequate dietary intake of protein affect albumin metabolism; they both result in decreased albumin synthesis, whereas inflammation alone is associated with increased fractional catabolic rate, and, when extreme, with increased transfer of albumin out of the vascular compartment. This explains why albumin administration to patients with hypoalbuminemia and chronic inflammatory diseases often has limited effects. Because serum albumin is a negative marker of inflammation, its value as a nutritional parameter in inflammatory disease states has been questioned.

We therefore adjusted models assessing the relationship between S. japonicum and albumin for CRP, a marker of inflammation. The inverse relationship between S. japonicum and albumin remained significant, suggesting that low albumin levels in our population may, in part, be caused by reduced protein intake caused by anorexia.

Egg antigens are the primary immune stimulant in schistosomiasis; thus, it was somewhat surprising to find a cross-sectional relationship between undernutrition and cytokine responses to SWAP but not to SEA. However, because treatment results in exposure of previously inaccessible worm proteins to the immune system, and we measured specific cytokine responses 4 weeks after treatment, this paradox may be explained by cross-reactivity between worm and egg antigens, because they display significant similarities.

Several limitations of this study should be addressed. First, evaluating mechanistic relationships within one model is complex. Our conclusions are based on separate relationships between S. japonicum, pro-inflammatory cytokines, and CRP and undernutrition. No definitive causal inference can be made based on these relationships. However, because we also assessed the relationship between schistosome-specific cytokines and undernutrition, we have strong evidence supporting a direct relationship between S. japonicum–induced cytokines and undernutrition. Second, because this study was primarily designed to assess immune correlates of resistance to reinfection, we lacked an uninfected control group at baseline. However, the N = 43 individuals in this cohort who did not become reinfected after treatment were regarded as controls in longitudinal analyses. Third, undernutrition can affect the immune response against parasitic infections, and thus may increase susceptibility to S. japonicum infection. Therefore.

### Table 3

Cross-sectional associations between cytokines produced in response to S. japonicum antigens and nutritional status at 4 weeks after treatment

<table>
<thead>
<tr>
<th>Cytokine Response</th>
<th>HAZ (Z-score)</th>
<th>BMIZ (Z-score)</th>
<th>UMAZ (Z-score)</th>
<th>SSFZ (Z-score)</th>
<th>Albumin (g/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln IL-1b to SEA</td>
<td>-0.01 (P = 0.81)</td>
<td>-0.02 (P = 0.67)</td>
<td>0.02 (P = 0.69)</td>
<td>-0.04 (P = 0.15)</td>
<td>0.11 (P = 0.62)</td>
</tr>
<tr>
<td>Ln IL-1b to SWAP</td>
<td>-0.04 (P = 0.30)</td>
<td>-0.03 (P = 0.29)</td>
<td>-0.03 (P = 0.35)</td>
<td>-0.01 (P = 0.38)</td>
<td>-0.54 (P &lt; 0.0001)</td>
</tr>
<tr>
<td>Ln TNF-α to SEA</td>
<td>-0.08 (P = 0.15)</td>
<td>0.00 (P = 0.95)</td>
<td>0.01 (P = 0.75)</td>
<td>-0.03 (P = 0.26)</td>
<td>0.04 (P = 0.83)</td>
</tr>
<tr>
<td>Ln TNF-α to SWAP</td>
<td>-0.10 (P = 0.045)</td>
<td>-0.06 (P = 0.13)</td>
<td>-0.04 (P = 0.30)</td>
<td>-0.02 (P = 0.22)</td>
<td>-0.39 (P = 0.006)</td>
</tr>
</tbody>
</table>

* Estimates represent mean difference per unit change in the log-transformed cytokine. All models were adjusted for cytokine level in response to control media, sex, age, and clustering at the household level.

HAZ, height-for-age Z-score; BMIZ, body mass index Z-score; UMAZ, upper-arm muscle area Z-score; SSFZ, sum of triceps and subscapular skinfolds Z-score; SEA, soluble egg antigen; SWAP, soluble worm antigen preparation.
reverse causality or a bidirectional relationship between *S. japonicum* and undernutrition cannot be excluded. However, subjects with severe malnutrition, in whom undernutrition-mediated immune suppression has been described, were excluded from participation in our study. In addition, we previously described that nutritional status improved after treatment in this cohort, attenuating the likelihood of reverse causality in this study.

In conclusion, our results suggest that *S. japonicum*-associated nutritional morbidity may, in part, be mediated by systemic inflammation; undernutrition in this context likely results from a combination of anorexia, metabolic changes, and body protein redistribution, leading to cachexia. Consequently, the potential effectiveness of nutritional supplementation alone to reduce nutritional morbidity in areas endemic for *S. japonicum* may be limited and should be combined with schistosomiasis control strategies.

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