Adjusting for the Acute Phase Response Is Essential to Interpret Iron Status Indicators among Young Zanzibari Children Prone to Chronic Malaria and Helminth Infections

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Abstract

The extent to which the acute phase response (APR) influences iron status indicators in chronic infections is not well documented. We investigated this relationship using reported recent fever and 2 acute phase proteins (APP), C-reactive protein (CRP), and α-1-acid glycoprotein (AGP). In a sample of 690 children matched on age and helminth infection status at baseline, we measured plasma for AGP, CRP, ferritin, transferrin receptor (TfR), and erythropoietin (EPO) and whole blood for hemoglobin (Hb) concentration, zinc protoporphyrin (ZPP), and malaria parasite density, and we obtained maternal reports of recent fever. We then examined the influence of the APR on each iron status indicator using regression analysis with Hb as the outcome variable. Ferritin was inversely related to Hb in the APR-unadjusted model. Adjusting for the APR using reported recent fever alone was not sufficient to reverse the inverse Hb-ferritin relationship. However, using CRP and/or AGP resulted in the expected positive relationship. The best fit model included reported recent fever, AGP and CRP (R² = 0.241; P < 0.001). The best fit Hb-ZPP, Hb-TfR, and Hb-EPO models included reported recent fever and AGP but not CRP (R² = 0.253, 0.310, and 0.292, respectively; P < 0.001). ZPP, TfR, and EPO were minimally influenced by the APR, whereas ferritin was immensely affected. Reported recent fever alone cannot be used as a marker for the APR. Either AGP or CRP is useful for adjusting if only 1 APP can be measured. However, AGP best predicted the APR in this population.

Introduction

WHO estimates that one-third of the world’s population is anemic and that ~50% of all anemias can be attributed to iron deficiency (1). This is often exacerbated by infectious diseases such as malaria, HIV/AIDS, and helminth infections. Together, iron deficiency and infectious diseases contribute to the high prevalence of anemia that mainly affects women and children (2,3). The consequences of iron deficiency in infants and children include impaired cognitive performance, impaired motor and language development, and reduced appetite (4–9).

Despite the public health burden of iron deficiency and anemia, ascertaining the validity of iron status indicators in populations prone to chronic infections remains problematic (10). In populations where iron deficiency is prevalent, many other nutritional and infectious processes may interfere with the interpretation of iron status indicators (11–13). Two commonly cited phenomena are hypoferremia of inflammation and the rise in ferritin concentrations. The host modifies iron metabolism to make iron less available for pathogens, resulting in a decline in circulating iron with the onset of inflammation (14). In addition, ferritin, an indicator of iron stores and a positive acute phase protein (APP), is elevated in a manner comparable to the other APP, C-reactive protein (CRP) and α-1-acid glycoprotein (AGP) (14,15). Thus, in a population with frequent exposure to endemic disease, infection may distort estimates of iron status. In Zanzibar, this distortion is more pronounced in younger children compared with school children or adults, because in these older populations, malaria infection is less frequently associated with symptomatic malaria disease (16,17).
To avoid such distortion, some investigators have sought to use iron status indicators that are less perturbed by infections or inflammation, such as transferrin receptor (TfR) (2). However, using a single iron status indicator depicts only one stage of iron depletion, such as tissue iron deficiency in the case of TfR (18). Therefore, to provide a precise quantitative measure of body iron over a broad range of iron status, multiple iron status indicators are needed (10) and so this enhances the need to correct for subclinical infection or inflammation.

To address this need, WHO and CDC recently called for more research on the best use of APP in addressing the influence of the acute phase response (APR) on iron status indicators in the context of chronic infections (10). APP provide an advantage because their concentrations in plasma change in response to any infection, even latent infections when there are no apparent clinical signs (19,20). Fevers are common in children living in the tropics and reported recent fever is simple to determine and is advantageous, because it does not involve drawing of blood. However, recent fever may not be an adequate marker of subclinical infections. We therefore endeavored to: 1) determine the relationship between chronic infections (malaria and helminth infections) and APP; 2) explore the relationship between APP and iron status indicators; 3) determine the concentration of iron status indicators in different stages of inflammation as defined by APP; and 4) determine to what extent adjusting for the APR (reported recent fever, AGP, and CRP) reveals the expected relationships between hemoglobin (Hb) concentration and iron status indicators (a positive Hb-tfRin relationship and inverse Hb-zinc protoporphyrin (ZPP), Hb-TfR, and Hb-erythropoietin (EPO) relationships).

Methods

Study site. The study was conducted in Wete District of Pemba Island, Zanzibar, United Republic of Tanzania. At the time of the study (2003–2004), P. falciparum malaria was highly prevalent (~80%), with no distinct evidence of seasonality (21). The soil-transmitted helminths Ascaris lumbricoides, Trichuris trichiura, and hookworm species (Ancylostoma duodenale and Necator americanus) are endemic in this population (22).

Study population. The study was conducted on archived plasma samples and data collected as part of a clinical trial designed to test the effect of early helminth infection on growth, anemia, inflammation, and appetite (International Standard Randomized Controlled Trial no. 83988447; R. J. Stoltzfus, H. J. Haji, V. J. Wright, D. Goodman, Q. Bickle, M. Ramsan, and J. M. Tielsch, unpublished data). The study recruited 2322 children aged 6–23 mo who were screened for helminth infections and were randomly allocated to mebendazole treatment (3-d course, 100 mg twice per day) or placebo repeated every 3 mo for a 12-mo period. To study inflammatory mechanisms, a subsample was constructed that was enriched in infected children. The subsample consisted of 230 age-matched triplets (690 children) selected on a 2:1 ratio according to their infection status at baseline (2 helminth-infected for 1 uninfected child). This paper is a cross-sectional analysis of the full biochemical results have similar characteristics to those with missing values for the analyses (data not shown).

Measurements of infections. Whole blood from the EDTA collection tube was used to prepare duplicate thick blood smears within 4 h of venipuncture. The blood film was left to air dry and stained with 10% Giemsa and studied for malaria parasites by microscopy. Approximately 100 fields were scanned and the numbers of parasites were counted up to 200 leukocytes. If the number of parasites was ≤9, the numbers of parasites up to 300 leukocytes were counted. The number of parasites per μL was calculated by number of parasites × 8000 divided by the number of leukocytes counted, where 8000 is the standard for the average number of leukocytes per μL and so allowed for a reasonable comparison between patients. Species determination was not undertaken, because previous research in this site has documented that P. falciparum is the nearly universal species (17,25).

Ascaris, hookworm, and Trichuris infections were diagnosed by examination of 3 stool samples using Kato-Katz and sedimentation methods to maximize detection of light infections (26). Duplicate Kato-Katz slides were made from stool samples collected over 2 d. The preparation of slides was according to the WHO protocol (27). The simple gravity sedimentation method was done as described by Goodman et al. (2007) (26). Recent fever was assessed by 5-d maternal recall using the local term for fever.

Statistical analysis. We analyzed the data using SPSS software (version 16.0). Ferritin, TfR, EPO, and CRP were normalized by log 10 transformation before analysis. Elevated APP concentrations were defined as AGP >1 g/L (28) or CRP >3 mg/L (29). A Hb cutoff of <100 g/L was defined as anemia and <70 g/L was defined as severe anemia (1). The anemia cutoff was lower than the WHO recommended cutoff for this age group.

TABLE 1 Demographic, infection, and biochemical characteristics in a sample of 6- to 2-mo-old Zanzibari children

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>±</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mo</td>
<td>654</td>
<td>17</td>
</tr>
<tr>
<td>Sex ratio (male:female), n:n</td>
<td>654</td>
<td>332.32</td>
</tr>
<tr>
<td>Malaria infection, %</td>
<td>154</td>
<td>24.5</td>
</tr>
<tr>
<td>Any helminth infection, %</td>
<td>453</td>
<td>70.1</td>
</tr>
<tr>
<td>Recent fever (past 5 d), %</td>
<td>285</td>
<td>43.6</td>
</tr>
<tr>
<td>Plasma CRP, mg/L</td>
<td>567</td>
<td>4.09 (1.73, 13.25)</td>
</tr>
<tr>
<td>Plasma AGP, g/L</td>
<td>294</td>
<td>156.84 ± 66.49</td>
</tr>
<tr>
<td>Hb, g/L</td>
<td>648</td>
<td>101.04 ± 15.74</td>
</tr>
<tr>
<td>ZPP, μmol/mol heme</td>
<td>512</td>
<td>184.07 ± 78.54</td>
</tr>
<tr>
<td>Plasma ferritin, μg/L</td>
<td>279</td>
<td>41.10 (23.80, 73.00)</td>
</tr>
<tr>
<td>Plasma TfR, mg/L</td>
<td>293</td>
<td>13.40 (10.65, 18.30)</td>
</tr>
<tr>
<td>Plasma EPO, IU/L</td>
<td>266</td>
<td>28.75 (17.30, 51.52)</td>
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</table>

1 Data are mean ± SD, median (IQR), or %.

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Results

Demographic, infection, and biochemical characteristics of the children. The age of the children was $17 \pm 4$ mo and

| TABLE 2 | Plasma concentrations of APP in a sample of 6- to 2-mo-old Zanzibari children by baseline helminth and malaria infection status$^1$
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Presence of helminths in the sub-sample$^2$</td>
<td>Presence of malaria in the sub-sample$^2$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$n$</td>
<td>No helminths</td>
<td>$n$</td>
<td>Any helminths</td>
<td>$P$</td>
<td>$n$</td>
<td>No malaria</td>
<td>$n$</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>AGP, g/L</td>
<td>95</td>
<td>$1.64 \pm 0.76$</td>
<td>194</td>
<td>$1.53 \pm 0.60$</td>
<td>0.184</td>
<td>194</td>
<td>$1.41 \pm 0.59$</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>154</td>
<td>4.39 [3.52, 5.47]</td>
<td>401</td>
<td>4.63 [4.08, 5.28]</td>
<td>0.665</td>
<td>393</td>
<td>3.54 [3.13, 4.01]</td>
</tr>
</tbody>
</table>

$^1$ Values are mean ± SD, geometric mean (95% CI), or %.

$^2$ Helminth APP were analyzed independent of malaria and malaria APP analyzed independent of helminth.

$^3$ APP data were log-transformed before analysis; untransformed data are presented.

50.8% were males. The prevalence of malaria infection was 24.5%, whereas by design, 70.1% of the children in the sample had 1 or more helminth infections. About two-fifths (43.6%) of the children reported fever in the 5 d prior to the interview date. The CRP concentration was 4.09 mg/L (1.73–13.25 mg/L) and that of AGP was 1.57 ± 0.66 g/L, indicating a high degree of inflammation in the study sample. The mean and median values of Hb and other iron status indicators were beyond the known cutoff limits (1) and therefore were strong indicators of a population with a high incidence of iron deficiency and anemia (Table 1).

**Chronic infections and the APP.** Children with malaria infection, with or without helminths, had higher plasma AGP ($P < 0.001$) and CRP ($P < 0.001$) compared with malaria noninfected children with or without helminths. In contrast, the
APP did not differ among children with or without any helminth infection (with or without malaria infection) (Table 2). In addition, the prevalence of elevated APP concentration [defined as AGP > 1 g/L (28) and CRP > 3 mg/L (29)] was higher in malaria-infected children compared with children not infected with malaria (P < 0.001) with or without helminths. This was not the case for helminth infections with or without malaria infection (Table 2).

**The association between APP and iron status indicators.** Ferritin was positively correlated with both AGP (r = 0.524; P < 0.001) and CRP (r = 0.515; P < 0.001) but inversely correlated with Hb (r = −0.189; P = 0.002) (Table 3). Other iron status indicators that are thought to be less perturbed by inflammation (ZPP, TfR, and EPO) were also correlated with AGP and CRP (P < 0.05 for all comparisons). However, the strength of the positive correlation with the APP was moderate (0.5 < r < 0.8) in the case of ferritin but weak (|r| ≤ 0.5) for the other iron status indicators.

Iron status indicators were also assessed by inflammation status of the children defined by APP “neither elevated,” “either elevated” or “both elevated.” It is noteworthy that the trend for ZPP (P = 0.030), ferritin (P < 0.001), TfR (P < 0.004), and EPO (P < 0.001) was consistently increasing across these categories and that the trend for Hb (P < 0.001) was in the opposite direction. The mean values did not differ between the subgroups “neither elevated” and “either elevated” (P > 0.05 for all comparisons). In the either elevated subgroup, 73 children had elevated AGP but not CRP and only 8 children had elevated CRP but not AGP. Because of the small number in the latter category, we did not have enough power to compare the APP singly (Table 4).

Overall, the prevalence of anemia and/or iron deficiency varied depending on the iron status indicator and cutoff used. Using a Hb cutoff of 100 g/L, 43.4% of all children were anemic. Even using the ferritin cutoff of 30 μg/L to account for prevalent inflammation, the percentage of children who were iron deficient as indicated by ferritin (35.5%) was still lower than that of those indicated by ZPP (85.3%) or TfR (93.8%) (Table 5). The percentages of anemic or iron-deficient children did not differ between the neither elevated or either elevated subgroups.

**The influence of the APP on the iron status indicators.** Nonparametric exploratory scatter plots revealed that at low values of log ferritin (<1.50 μg/L), Hb was directly (i.e., positively) related to log ferritin (Fig. 1A). This is the expected relationship if low ferritin is reflecting iron deficiency. However, at high values of log ferritin, the direct relationship changed to an inverse relationship. The Hb-log ferritin infection point (1.50 μg/L) corresponds to the commonly cited cutoff for iron deficiency using ferritin in the presence of inflammation (30 μg/L).

In simple linear regression of Hb on ferritin, the slope of the line was negative, reflecting the majority of the data, which were to the right of the infection point (Fig. 1B). We then adjusted for the APR in a stepwise manner by sequentially adding reported recent fever, CRP, and AGP. Adding reported recent fever had only a slight effect on the slope. However, adjusting for either AGP or CRP reversed the inverse relationship to a positive iron deficiency relationship (Fig. 1B). The best fit model retained reported recent fever, AGP, and CRP and their interactions with ferritin, although the main effects of reported recent fever and CRP and their interactions with ferritin were not significant (reported recent fever main effect, P = 0.911; interaction, P = 0.547; and CRP main effect, P = 0.600; interaction P = 0.307), whereas the main effect of AGP and the ferritin by AGP interaction were significant (main effect, P = 0.109; interaction, P = 0.046) (R² = 0.241; P < 0.001).

**TABLE 5** Prevalence of anemia and iron deficiency in a sample of 6- to 23-mo-old Zanzibari children according to their inflammation status defined by plasma AGP and plasma CRP

<table>
<thead>
<tr>
<th>Anemia and iron deficiency</th>
<th>All children</th>
<th>Neither elevated</th>
<th>Either elevated</th>
<th>Both elevated</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemic (Hb &lt;100 g/L), %</td>
<td>43.4 (109/251)</td>
<td>33.3&lt;sup&gt;a&lt;/sup&gt; (12/36)</td>
<td>32.6&lt;sup&gt;a&lt;/sup&gt; (26/80)</td>
<td>52.6&lt;sup&gt;c&lt;/sup&gt; (71/135)</td>
<td>0.007</td>
</tr>
<tr>
<td>Severely anemic (Hb &lt;70 g/L), %</td>
<td>6.0 (15/251)</td>
<td>0&lt;sup&gt;b&lt;/sup&gt; (0/36)</td>
<td>2.5&lt;sup&gt;c&lt;/sup&gt; (2/80)</td>
<td>9.6&lt;sup&gt;c&lt;/sup&gt; (13/135)</td>
<td>0.027</td>
</tr>
<tr>
<td>Low ferritin (&lt;30 μg/L), %</td>
<td>35.5 (87/245)</td>
<td>63.9&lt;sup&gt;d&lt;/sup&gt; (23/36)</td>
<td>47.9&lt;sup&gt;c&lt;/sup&gt; (34/71)</td>
<td>21.7&lt;sup&gt;c&lt;/sup&gt; (30/138)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High ZPP (&gt;120 μmol/mol heme), %</td>
<td>85.3 (191/224)</td>
<td>80.0&lt;sup&gt;d&lt;/sup&gt; (28/35)</td>
<td>77.9&lt;sup&gt;c&lt;/sup&gt; (53/68)</td>
<td>90.9&lt;sup&gt;d&lt;/sup&gt; (110/121)</td>
<td>0.034</td>
</tr>
<tr>
<td>High TfR (&gt;8.3 mg/L), %</td>
<td>88.8 (242/258)</td>
<td>84.2&lt;sup&gt;d&lt;/sup&gt; (32/38)</td>
<td>95.1&lt;sup&gt;c&lt;/sup&gt; (77/81)</td>
<td>95.7&lt;sup&gt;c&lt;/sup&gt; (133/139)</td>
<td>0.029</td>
</tr>
</tbody>
</table>

<sup>1</sup> Values are % (n/total n). Subgroup percentages in a row without a common letter differ, P < 0.05 (χ² test).
In general, Hb was inversely related to ZPP (Fig. 2). Adjusting for the APR, the predicted relationship at the 10th percentile of the APP revealed an upward shift in the y-intercept (by 9.3 g/L Hb) but did not change the slope much. In other words, after adjusting for the APR, the predicted value of Hb for a given ZPP was 9.3 g/L higher, but the relationship between the variables was otherwise unchanged. The best fit model had reported recent fever and AGP but no CRP (R^2 = 0.253; P < 0.001) (Fig. 2B).

Lastly, both the Hb-TfR and Hb-EPO scatter plots and their predicted relationships at the 10th percentiles of CRP or AGP were in the inverse direction, as expected. Adjusting for the APR changed the slopes slightly. The best fit Hb-TfR (Fig. 3) and Hb-EPO (Fig. 4) models had reported recent fever and AGP but no CRP (R^2 = 0.310 and 0.292, respectively; P < 0.001).

**Discussion**

The measurement of Hb is widely used in nutritional surveys to screen for anemia as a proxy for iron deficiency because of its simplicity and low cost (31). However, Hb does not distinguish between iron deficiency anemia and anemia of inflammation (10). In the absence of inflammation, ferritin is thought to be the most sensitive indicator for iron deficiency, although its usefulness in the presence of inflammation is questionable. Ferritin is a positive APP that is elevated during an APR. TfR has been promoted as the iron status to use in the presence of inflammation; however, because it is affected by the rate of erythropoiesis, age -cutoffs are still urgently needed (32,33). ZPP assay can easily be performed on whole blood or dried spots; however, like EPO and TfR, these indicators can be elevated by malaria or other chronic infections (17,32,34,35). Because of the potential disadvantages of iron status indicators, there has been no agreement on the best laboratory criteria for the assessment of iron deficiency in populations with prevalent inflammation. WHO/CDC has proposed the use of multiple iron status...
indicators and has called for more research on best ways to account for the influence of inflammation (10).

To deal with the influence of the APR on iron status indicators, a number of approaches have been used. In the first approach, the cutoffs of the iron status indicators have been adjusted to account for this influence. For instance, in children <5 y, the suggested cutoff for ferritin shifts from the normal 12–15 mg/L cutoff to 30–50 mg/L (36). This is problematic because it does not provide a distinct international standard. Additionally, it is difficult to arrive at a single cutoff because of varying degrees of inflammation. In a second approach, some authors have excluded individuals with inflammation from analysis. This approach may reduce the sample size significantly, especially in developing countries where many asymptomatic individuals have chronic inflammation (17,37). It can therefore result in biased findings. A third approach proposed more recently involves deriving correction factors by dividing the reference median value by the median for the respective groups with raised APP (38). Although this approach seems promising, the usefulness of this formula has not been confirmed by other researchers. Also, the authors admit that not all surveys will produce a reference group of sufficient sample size to calculate reliable correction factors (39). Furthermore, this approach does not specify which marker of the APR is ideal.

Because the above 3 approaches have drawbacks, we attempted to adjust for the influence of the APR on iron status indicators by regression modeling. From our initial analysis, the APR in this age group was predominantly driven by malaria infection, which was found to be proinflammatory, in contrast to helminth infection. We initially theorized that helminth infections would be proinflammatory (Th1 response) in these children, with primary infection based on experiments on mouse model strains that have been shown to induce Th1 responses to primary infections as opposed to polarized Th2 responses typical of helminthiasis (40).

The relationship between Hb concentration and iron status indicators

Hb vs. ferritin. Ferritin is linearly related to iron stores in healthy individuals (41). Therefore, in a situation where children do not have chronic infections, we expect to see those with high values of Hb having concomitant high ferritin concentrations. In the present study, the best fit model that depicts this relationship has both AGP and CRP as continuous variables with the calculated 10th percentile of the APP. Reported recent fever alone as a marker of the APR was not sufficient to adjust for the influence of the APR on ferritin. This finding is important especially for nutritional surveys where no APP is measured.

During an acute infection, ferritin increases rapidly and in parallel to CRP (15), whereas during a chronic infection, ferritin...
behaves more like AGP, which remains elevated as clinical symptoms disappear because ferritin has a longer time course than CRP (15, 42, 43). The degree to which ferritin increases is influenced by the underlying iron status (44), whereas the rise in the APP is related to the severity of infections (45). Because iron status and severity of infection fluctuate significantly within and between individuals, it is difficult to quantify the APP or iron status using ferritin alone during both acute and chronic infections. In the initial phase of infection, CRP may better predict the behavior of ferritin, whereas in the later stages of inflammation, AGP is a better predictor of the influence of the APP on ferritin (42). Although we theorized that the children in our study had chronic infections, it is likely that they may have had undetected acute infections and hence the necessity of both APP to adjust for the influence of the APR.

Unlike a previous study in Zanzibari school children where ferritin was directly (i.e., positively) related to Hb regardless of malaria parasitemia (17), in the young children we studied, ferritin was inversely related to Hb before adjusting for the APR. This is because prevalent subclinical infection simultaneously drives down Hb and drives up ferritin.

Hb vs. ZPP, TfR, and EPO. The direction of the predicted relationship between Hb and ZPP, TfR, and EPO was not influenced by the APR (Figs. 2–4). This is consistent with the current thinking that these iron status indicators are less perturbed by inflammation than is ferritin. In addition, although a positive correlation was noted between these iron status indicators and the APP, the strength of these correlations were weak.

Although TfR is not directly increased by the APR, it is thought to be indirectly decreased by inflammation because of reduced EPO production and suppression of erythropoiesis by cytokines (32). Both ZPP [which is a product of disordered heme biosynthesis (46)] and EPO [the hormone which regulates erythropoiesis (47)] were also inversely related to Hb.

Based on our observations that the APR slightly shifted the magnitude of the relationship between Hb and ZPP, TfR, and EPO but did not change the direction of the relationship as in the case of ferritin, we think that the influence of the APP on ZPP, TfR, and EPO is relatively small. However, the 9.3 g/L Hb shift in the y-intercept in the case of ZPP might be large enough to cause more frequent overdiagnosis of iron deficiency.

In conclusion, ZPP, TfR, and EPO were minimally influenced by the APR, whereas ferritin was immensely affected. Reported recent fever alone cannot be used to adjust for the APR in nutritional surveys, even where fevers are common. The best fit Hb-ferritin model had reported recent fever, AGP, and CRP, whereas the best fit Hb-ZPP, Hb-TfR, and Hb-EPO models had reported recent fever and AGP but no CRP. We therefore recommend the use of multiple markers of the APR to adjust for its influence on iron status indicators. If only 1 APP can be measured, either AGP or CRP is useful. However, AGP best predicted the APR in a population with prevalent and chronic inflammation.

Acknowledgments
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Literature Cited


