Iron Metabolism, Malaria, and Other Infections: What Is All the Fuss About?1,2

Andrew M. Prentice*

MRC International Nutrition Group, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK; and MRC Keneba, The Gambia

Abstract

This article briefly describes how iron lies at the center of a host-pathogen battle for nutrients and why there are many theoretical reasons to suspect that administration of supplemental iron might predispose to infection. This is supported by in vitro and small animal studies, but meta-analysis of human epidemiological and intervention studies has found little evidence for most disease outcomes. Supplemental iron does appear to increase susceptibility to malaria as measured by a variety of malarialometric indices. However, even in malarious areas, iron appears beneficial in iron-deficient subjects. The concerns about iron supplementation programs for children seem to be confined to Sub-Saharan Africa and to areas of high malaria endemicity, where it will be necessary to adopt a cautious approach to supplementation based either on screening out iron-replete children or combining iron administration with effective disease-control strategies. J. Nutr. 138: 2537–2541, 2008.

Introduction

Iron deficiency and iron deficiency anemia (IDA) are estimated to be the most widespread of all nutritional deficiencies (1), and, as a consequence, iron is probably the most widely administered of all compounds both through preventative campaigns involving mass administration and by individual prescription. WHO and International Nutritional Anemia Consultative Group guidelines for combating IDA have been widely adopted by most less-developed countries, and efforts to enhance the efficiency of implementation were gathering pace until results of the Pemba trial, showing an increase in serious adverse events among children receiving iron, were published (2) and then widely publicized. Because Pemba is an area of hyperendemic malaria, and because a very similar trial in malaria-free Nepal found no such adverse effect (3), the result has been generally ascribed to an adverse interaction between iron administration and malaria. As discussed by Stoltzfus in an accompanying article (4), the detrimental effect was confined to children who were iron replete, suggesting that it is an excess of iron that generated the adverse interaction.

This article examines the issues surrounding iron and infections with special attention to malaria.

The critical role of iron in host and pathogen biology

There are multiple reasons to conclude that, among the 40 or so nutrients essential to human health, iron plays the most critical role in relation to the host’s interactions with pathogens (viruses, bacteria, and protozoa) (5,6). In brief the evidence can be summarized as follows (see also Fig. 1): 1) although iron is a highly abundant element, it is highly insoluble at physiological pH and in the oxidative conditions of life, and therefore, it is difficult to acquire; 2) iron has very useful redox characteristics that have resulted in its incorporation in a very wide range of enzyme and oxygen transport systems; 3) these same redox characteristics also make free iron potentially very harmful because of the generation of free radicals; 4) humans have evolved a range of transport, sequestration, and storage systems for iron (e.g., transferrin, lactoferrin, ferritin, haptoglobin, hemopexin) that appear well adapted to prevent iron causing localized tissue damage; 5) these systems are up-regulated by the acute-phase response to infection causing a depletion of iron in the systemic circulation down to \(10^{-24}\) mol/L (teleologically interpreted as a defense mechanism by depriving pathogens of iron); 6) both in vitro and in vivo (small animal) experiments clearly demonstrate that addition of iron (in various forms including as heme) overcomes the bacteriostatic and bacteriocidal effects of iron-binding proteins; 7) in response to these human adaptations, bacteria, in particular, have evolved an astonishing range of siderophores and related iron acquisition molecules with very strong iron-binding capabilities (e.g., \(10^{-52}\) mol/L for enterobactin); 8) in many bacteria, the so-called “islands of high pathogenicity” within their genome are enriched in iron acquisition genes; and 9) genetic detective work strongly indicates that microorganisms have had to acquire specialist methods for iron retrieval before they could colonize humans.

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* To whom correspondence should be addressed. E-mail: andrew.prentice@lshtm.ac.uk.
These factors combine to place iron at the center of the host-pathogen battleground for nutrients and suggest that optimizing iron status may involve a very delicate balance; a deficit of iron will impair host function (including immunity), but an excess may favor the growth and pathogenicity of microorganisms (7). This is the biological background against which we should judge the epidemiological evidence linking iron administration to an increased susceptibility to infections.

Iron and infections: what is the evidence?

The data from Pemba suggesting that iron administration can increase a person’s vulnerability to infection are by no means new. As long ago as the 1850s, the Parisian physician Trousseau warned his students of the mortal consequences of administering iron to TB patients (8), and there are much-quoted data suggesting that refeeding malnourished refugees and consequent hyperferremia caused a recrudescence of malaria and other infections (9,10). In consequence of these and other data, the WHO Guidelines for Treatment of Severely Malnourished Children advise withholding of iron until wide-spectrum antibiotics have been used to control bacterial infections. There is also emerging evidence to suggest that iron plays diverse roles in viral infections (11), and we have recently shown that elevated ferritin levels strongly predict earlier mortality in HIV patients (12).

To examine whether these occasional findings are supported by the totality of evidence, Gera and Sachdev (13) conducted a meta-analysis of 28 randomized controlled trials of iron intervention. Outcomes were “all infections,” respiratory tract infections, diarrhea, and malaria. Risk of diarrhea was found to be marginally significantly elevated with a relative risk of 1.11 (95% CI 1.01–1.23). The risk of other infections was not significantly altered.

Results of the Pemba and Nepal trials (2,3) were not available when the Gera meta-analysis was conducted. Stoltzfus et al. (14) have since updated and critically reviewed the evidence on possible effects of iron and iron plus folic acid on infections and included both the Pemba and Nepal main studies and the Pemba substudy. Their summary indicates that the evidence for harmful effects is minimal. In particular, the very marginal negative effect on diarrhea noted in the Gera summary is offset by slight (but nonsignificant) protective effects in Pemba and Nepal.

There has been 1 further trial published since the Stoltzfus review. This examined the effects of iron supplementation on incidence of malaria in Peru and showed a 49% increase in malaria episodes (Plasmodium vivax) in children over 5 y of age but had no significant effect on diarrhea or respiratory tract infections in any age group (15).

Meta-analyses such as these should be interpreted with caution because most of the studies included have not disaggregated their data according to the baseline iron status of the children. The Pemba substudy analysis indicates that positive effects in iron-deficient children may be balanced by negative effects in iron-replete children, thus tending toward a neutral result within any population that contains a range of iron status. It is critical that future study designs and analysis plans take into account iron status.

Iron and malaria

Following the Pemba trial a key question facing researchers is: “What are the potential mechanisms by which iron status could affect parasite invasion or growth and hence the clinical sequelae of infection?” Most discussion of this question revolves around the blood stages of the parasite with virtually nothing known about factors that might impact on the liver stages, and this would be an important target for future research. At present there are 4 regularly cited suggestions as to possible means by which iron status might influence susceptibility to malaria.

The first is simply through alterations in iron availability for parasite growth and replication. In its erythrocytic stages, the
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The malaria parasite presents some paradoxes in relation to its iron acquisition. Heme iron, although available in abundance, appears not to be utilized by plasmodia and must be detoxified through formation of the hemazoin complex, which contains 2.2 mol/L iron (16). It appears that the parasite is dependent on the very small pool of labile iron in the cytoplasm and hence might be sensitive to external (nutritional) influences on the concentration of iron in this compartment (16).

A second possibility is that iron supplementation might enhance susceptibility by stimulating erythropoiesis because there is evidence that parasites have a preference for reticulocytes. However, this is only true of \( \textit{P. vivax} \) and would not explain effects on \( \textit{P. falciparum} \) as has sometimes been erroneously claimed.

A third possibility is that zinc protoporphrin (a product of iron-deficient erythropoiesis) may inhibit hemozoin formation and hence generate a toxic environment in a manner analogous to an antimalarial drug action (17).

The final possibility would be through iron’s influence on host immunity.

**Epidemiological and intervention evidence linking iron and malaria**

Surprisingly, there have been rather few studies examining whether iron-deficient/anemic individuals are more or less vulnerable to malaria (Fig. 2). Two studies showed an increased susceptibility to malaria in individuals with high serum ferritin (18,19). Other studies have shown both increased (20) and decreased (21) susceptibility associated with higher hemoglobin levels. Confounding in such studies can easily arise from different proportions of hemoglobinopathies, which might be associated with both hemoglobin and protection from malaria.

The evidence from iron supplementation trials is more robust (Fig. 3) and has been reviewed in detail elsewhere (22–24). Of 15 studies reviewed most recently (24), 6 showed no effect of iron supplements on malaria risk; of these, 3 included large proportions of anemic subjects (74–94%), and 1 only included children with Hb <50 g/L. Other studies that stratified by baseline hemoglobin level found that the greatest benefits occurred in the most anemic subgroups, a finding that is in line with Stoltzfus’s interpretation of the Pemba data (4). Three studies showed an increase in clinical malaria attacks in the iron-supplemented groups and a further 6 studies found nonsignificant increases in malaria outcomes. One of the striking differences between study populations with significant increases in malaria outcomes and those with nonsignificant effects is access to health care and active treatment of malaria incident cases. In fact, all but 1 of the trials that found no effect on malaria outcomes provided access to health care facilities or active follow-up and treatment of malaria incident cases. This implies that the potential detrimental effects of iron supplementation may be curtailed by concurrent effective treatment of malaria infections. However, Verhoef et al. (25) and Nwanyanwu et al. (26) have shown potential treatment failure effects of combining sulfadoxine/pyrimethamine (SP) with iron in the treatment of preexisting malaria, suggesting that antimalarial therapy should precede supplementation.

In summary, the data from Pemba are generally in line with other studies that have previously hinted at likely detrimental effects of iron administration but have been able to show the adverse effects with much greater certainty as a consequence of the very large sample size.

**Balancing risks and benefits—other pros and cons of iron administration**

**Anemia.** Anemia is by far the most common clinical and epidemiological indicator for preventative and/or therapeutic iron, and there is no doubt that, under almost all conditions, administration of iron (given with or without folic acid, and sometimes with vitamin B-12) does achieve an increase in hemoglobin. However, effect sizes of <1 SD are usual, and this generally leaves a residual deficit of ~1 SD compared with well-nourished women and children from affluent populations even when treatment is combined with antihelmintics and antimalarials. The reason for the residual deficit is unclear.

**Effects on cognition and development.** The positive and lasting effects of iron on the mental and motor development of infants and children are reviewed in the accompanying paper from this symposium by Beard (27).

**Iron and oxidative stress/tissue damage.** Animal studies appear to confirm the theoretical concerns that excess iron may induce oxidative damage as measured by increases in lipid peroxidation, DNA damage, and colitis. Human studies also show evidence for raised thiobarbituric acid reactive substances when iron is given at >60 mg/d, that iron chelation can decrease thiobarbituric acid reactive substances, and that iron stores correlate with DNA damage.

**Effects on growth.** In a meta-analysis of 25 studies (19 supplementation, 6 fortification) Sachdev et al. (28) showed very small and mostly nonsignificant effects of iron on growth. Weight-for-age was increased by 0.13 SD \((P = 0.04, \text{nonsignificant after adjustments})\), and height-for-age was unaffected. Disaggregation of the data showed a positive effect on weight-for-age in malarious areas and a negative effect on height-for-age in developed countries when iron was given for longer than 6 mo.

Two studies have been widely quoted as raising concerns relating to iron and growth (29). In Swedish infants there was a significant decrease in length and head circumference between 4 and 9 mo in the group receiving iron (29). A study of Honduran infants by the same investigators showed decreased length (4–6 mo) in iron-replete subjects (29). This latter finding has been confirmed by a study from India (30).

**Putative interactions with zinc and copper metabolism.** Theoretical concerns that iron administration may inhibit absorption of copper and/or zinc were widely held some years ago but have not been confirmed. However, there is evidence that iron supplementation may interfere with copper utilization in malaria control trials and that zinc and copper are important for the immune system. Further research on these interactions is needed.

**Observational studies: Iron status and susceptibility to malaria**

- Early studies in famine environments: \( \text{†} \) malaria when iron-rich diets were introduced (Murray 9,10)
- Two studies (Snow 18, Nyakeriga 19) show \( \text{†} \) susceptibility to malaria in individuals with high serum ferritin
- Other studies show \( \text{†} \) (Oppenheimer 20) and \( \text{†} \) (Shipton 21) risk of malaria with higher Hb

Additional confounding can result from high proportions of hemoglobinopathies in the population

**FIGURE 2** Observational studies: Iron status and susceptibility to malaria.
ago but have not been borne out by experimental data and hence have largely subsided.

Summary of the critical issues

In summary, iron lies at the center of the host-pathogen battle for nutrients, and there are many theoretical reasons to suspect that extra iron might predispose to infection. This is supported by in vitro and small animal studies, but meta-analysis of human epidemiological and intervention studies has found little evidence for most disease outcomes. Supplemental iron does appear to increase susceptibility to malaria as measured by a variety of malarial indices. However, even in malarious areas, iron appears beneficial (strongly so) in iron-deficient subjects. The concerns about iron supplementation programs for children seem to be confined to Sub-Saharan Africa and to areas of high malaria endemicity, where it will be necessary to adopt a cautious approach to supplementation based either on screening out iron-replete children or combining iron administration with effective disease control strategies.

Other articles in this symposium include references (1,4,27,31).

Literature Cited