

Iron & Disease - Section 3

Iron supplementation in low-income countries

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Take Home Messages

- Iron deficiency anaemia (IDA) is the most common nutritional disorder worldwide and affects an estimated 1.2 billion people.
- Iron supplementation should be a practicable intervention in low-income countries but has very low efficacy and may cause harm by promoting infections.
- In the past 3 years the most likely mechanism by which iron supplementation increases malaria infection has been identified and reasons for the low efficacy are becoming clearer.

Introduction

The latest systematic analysis for the Global Burden of Disease Study 2016¹ estimated that 1.224 billion people worldwide suffer from iron deficiency anaemia (IDA). The consequences of iron deficiency (ID) and its associated anaemia are profound, ranging from early-life impairments in brain development, immune suppression and adverse pregnancy outcomes to lost productivity. IDA causes more years lived with disability than all other nutritional deficiencies, haemoglobinopathies and haemolytic anaemias combined.¹ It is the leading cause of disability in many low- and middle-income countries (LMIC) and in most of sub-Saharan Africa.

IDA is usually ascribed to poor quality diets containing low amounts of bioavailable iron and high levels of anti-nutrients such as phytates and phenols (primary dietary iron deficiency), and/or infections such as malaria and intestinal parasites (secondary deficiency). Increasing the dietary diversity of poor populations is recommended as the optimal option for overcoming primary deficiency but is impractical in most settings due to cost. As the world's population continues to rise it will also become increasingly difficult to provide the high quality (animal-based) foods that contain highly available iron. Thus supplementation with chemical forms of iron has been recommended for many decades as a pragmatic alternative and the World Health Organisation (WHO) recommends universal supplementation in population groups with a high prevalence of ID and IDA.^{2,3} However, iron supplementation programmes in LMICs suffer from low efficacy and evidence of harm.⁴⁻⁶

Current state-of-the-art

Debates around the safety and efficacy of iron supplementation in LMICs have raged for the past decade since the publication of the, now infamous, Pemba Trial that was stopped prematurely by its data and safety monitoring board due to evidence of significant harm in the groups receiving iron.⁴ Other randomized

trials have also reported evidence of harm^{5,7,8} and the problem has been widely debated. The latest research outputs on this topic are summarized below.

Malaria

The surprising evidence from epidemiological studies in children and pregnant women that IDA actually protects against malaria^{9,10} has been confirmed in *ex vivo* studies of *Plasmodium falciparum* parasite invasion and growth rates in red blood cells (RBCs) from anaemic children¹¹ and pregnant women.¹² These studies have also described the most likely mechanism by which iron supplementation increases the risk of malaria; namely that *P falciparum* grows much better in reticulocytes and large young RBCs than in mature cells, particularly the prematurely-aged cells of iron deficiency anemia.¹³ This is true both for laboratory and wild strains of the parasite. Remarkably it has been calculated that IDA offers much greater population protection against malaria than sickle cell trait.¹²

Gut dysbiosis

Recent work by Zimmermann's group at ETH Zurich, has consolidated their earlier demonstration that even low levels of iron as a fortificant (or as a supplement) can suppress the growth of beneficial gut organisms (lactobacilli and bifidobacteria) and enhance the growth of potential pathogens, as well as increasing gut inflammation.^{5,14} This represents a major challenge to iron supplementation programs and may explain observations in several studies that iron administration increases diarrhea. It might also explain some of the low compliance to iron supplements ascribed to gastric discomfort.

Importantly the same group have shown that the co-administration of prebiotic galacto-oligosaccharide (GOS) with iron mitigates the adverse effects of iron on the gut microbiome¹⁵ and also enhances the absorption of iron.¹⁶ If replicated in further studies this would appear to offer a promising way forward. An alternative, or complementary, approach would be to design iron compounds that retain their bioavailability for humans but are

unavailable to the gut microbiota. One such compound, iron hyroxide adipate tartrate¹⁷ is currently undergoing trials in rural African children.

Debates about the efficacy of iron supplementation

Numerous recent randomised trials with various formulations of iron supplements or point-of-eating food fortification (usually within multiple micronutrient powders) have shown very poor efficacy against ID and IDA.^(18,19) It must be assumed that the effectiveness of real-world programs would be even worse. Meta-analyses of trials in young children indicate a rise in hemoglobin of only between 3 and 5 g/L.^{3,20} Figure 1 shows that this would achieve only a very small correction of the hemoglobin deficit shown by typical rural African children. The benefit looks a little more impressive when quoted as a reduction in the proportion of children below the anemia cut-off of 110 g/L and hence these numbers are often cited. However, Verhoef *et al.*¹⁹ have argued that the public health gain from such programs must be measured using the continuous variable of hemoglobin because the dichotomous metric of anaemia percent over-emphasizes the benefit.

New insights from hepcidin biology

The discovery of hepcidin and the emergent understanding of its regulation and effector actions are providing critical new insights into the challenges surrounding iron supplementation in low-income countries.²¹ In brief, because hepcidin inhibits intestinal iron absorption and is itself upregulated by inflammation,²² it can cause a complex 'secondary' anemia of inflammation that co-exists with primary dietary iron deficiency. This has numerous implications both for the assessment and classification of ID and IDA,²¹ and for their prevention and treatment (discussed below).

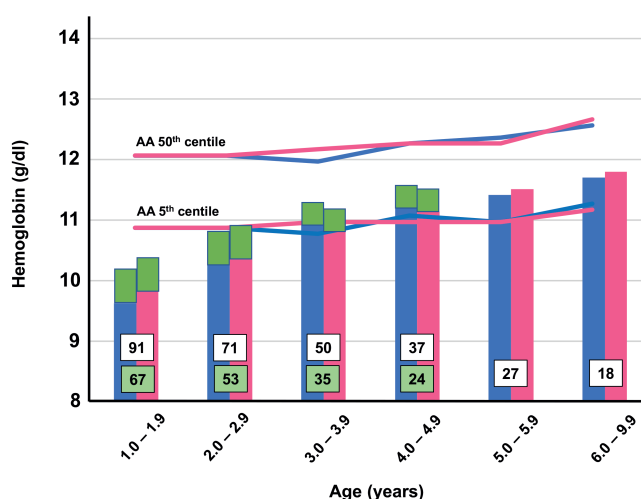


Figure 1. High levels of anemia in rural African children compared to their African-American counterparts. Data from 4239 children in the Keneba Biobank, West Kiang region of rural Gambia. Blue, boys; pink, girls. Numbers in white boxes are percent anemic (<11 g/dL). AA, African-American children from NHANES. Green bars show predicted increase in mean hemoglobin with supplementation of iron-containing multiple micronutrient powder (MMP) based on the WHO meta-analysis of RCTs in children 6-23 m and 2 to 12 years. Numbers in bars show percentage with anemia and those in green boxes show the estimated prevalence of anemia after supplementation based on the WHO meta-analysis.

Future perspectives

Given the harmful effects of ID/IDA and its enormous world-wide prevalence there is an urgent need to find really effective new solutions and to solve the policy impasse. Our research team has recent evidence that even very low-grade inflammation leads to hepcidin-mediated blockade of iron absorption in young African children living in unclean environments. These fresh insights, driven by the discovery of hepcidin, have potentially important implications for breaking through the roadblock of poor efficacy.

Ultimately, they demonstrate that in the special case of iron, whose absorption is so exquisitely regulated, nutrition-specific interventions will not succeed in the absence of so-called nutrition sensitive interventions to clean up children's living conditions and markedly reduce their levels of inflammation.

On the pathway to this end there are some clear intermediary research questions to be examined. What are the underlying causes of the inflammation? Surprisingly our data reveal no signal from the gut but very strong signals from fevers and respiratory illnesses. Is it possible to devise any safe anti-inflammatory interventions ahead of the ultimate goal of achieving western standard living conditions? Finally, might orally-active hepcidin antagonists one day emerge as new tools against ID and IDA in low income settings?

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