Does iron let boys grow faster?!

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Iron is an essential nutrient for the body as it plays a part in multiple enzymatic processes, including DNA synthesis, mitochondrial respiration, oxygen transport, hormone formation, and cellular metabolism.[1] Iron deficiency and iron deficiency anemia (the latter arising from limited availability of the metal for heme biosynthesis) are global health problems that affect around two billion people. These are particularly important in infants because they have a negative impact on children's growth and mental development.[2] Such a situation is highly prevalent in developing countries. Thus, efforts have been made to substitute iron to avoid such developmental defects in children. However, the unbiased administration of iron supplements to children's diets in tropical regions resulted in a significant increase in morbidity and mortality from infectious diseases.[3] These can be attributed to the fact that iron is an essential nutrient also for most pathogens but also impacts on the efficacy of anti-microbial immune effector pathways.[4,5] Subsequent studies have shown that mild iron deficiency in infants even offers protection from specific infections such as severe malaria.[6] This has left physicians with the dilemma as to how to identify children who may benefit from iron supplementation while avoiding the risk of an adverse outcome from infection.

Thus, several diagnostic approaches have been adopted to identify those children who may respond to iron supplementation therapy. In this context, the determination of the iron hormone hepcidin has attracted great interest. Hepcidin is a liver-derived peptide which controls body iron homeostasis upon binding to the only known cellular iron export protein ferroportin, resulting in its internalization and degradation.[1] Hepcidin expression is induced by body iron loading or inflammatory signals, including those arising from systemic infections, whereas iron deficiency (as well as, among others, hypoxia and anemia) reduce hepcidin expression.[7] Accordingly, low hepcidin levels enable dietary or orally supplemented iron to be absorbed from the duodenum, whereas high-circulating hepcidin levels impair iron transfer from duodenal enterocytes to the circulation.[8] In other words, subjects with true iron deficiency efficiently absorb iron from the duodenum, whereas persistent inflammation impairs iron uptake from the gut with iron remaining in the intestine.[8] This not only results in a blunted response to oral iron therapy, but also increases the availability of iron for the intestinal microbiome. This leads to subtle alterations of the composition of the microbiota with an increase in pathogenic bacteria and promotion of intestinal inflammation.[9] Thus, hepcidin determination in children has been seen to be a reliable diagnostic test to predict the response to oral iron therapy.[10] This is also of interest as infection inducible inflammatory signals impact on cytokine formation and stimulate hepcidin production, resulting in the development of functional iron deficiency, particularly in countries with a high endemic burden of infectious diseases. This functional iron deficiency is characterized by iron retention in reticuloendothelial cells and the emergence of anemia of inflammation or anemia of chronic disease which poorly responds to oral iron.[11] However, in tropical countries, due to nutritional iron deficiency and/or chronic blood loss on the basis of intestinal infestation with hookworms, counter-regulatory factors can impact on hepcidin levels. Studies in animal models have shown that the inhibitory signals exerted by iron deficiency dominate over hepcidin induction by inflammation.[12] This has also been confirmed in clinical trials in young women and in patients with inflammatory bowel disease and low-grade inflammation showing good absorption of oral iron.[13,14] This would suggest that low hepcidin levels, even in an inflammatory setting, would predict sufficient oral iron absorption.

To gain greater insight into how hepcidin levels are regulated and affected by different factors in a primary care setting, and how these change in early infancy over time, Armitage and co-workers analyzed data from two birth cohorts in The Gambia, Western Africa, adopting a longitudinal approach to the analysis.[15] They took repeat measurements of serum concentrations of hepcidin, iron, the iron storage protein ferritin, and soluble transferrin receptor (sTfR) (which is a marker for the needs of iron for erythropoiesis) and studied the results for associations of these markers with birth weight, growth, seasonality, infection, anemia, and nutrition. Children were investigated from birth until one year of age. First, the authors observed that low iron and hepcidin levels at birth were associated with a lower birthweight, pointing to the importance of sufficient maternal iron supplementation during pregnancy. Second, they also found a decrease in hepcidin, iron and ferritin levels over time which is indicative for incorporation of the metal into the growing body. Of note, a greater weight gain was associated with more severe iron deficiency as reflected by low ferritin and hepcidin levels. This also indicated that the faster growth of children is paralleled by or even a consequence of more efficient incorporation of iron in the body where it is used for erythropoiesis and enzymatic complexes including myoglobin in muscle cells. However, such faster growing children are more likely to become iron deficient because dietary iron availability cannot compensate for the increased incorporation of iron in the body. Thus, such children need specific attention in order to avoid unwanted negative effects of iron deficiency on their development from one year of age onwards; based on the data presented by Armitage *et al.*,[15] these infants can be identified by low hepcidin levels at the age of 12 months, but this also predicts that they will respond to oral iron therapy.

Most surprisingly, the significant association between growth promotion and iron deficiency was most pronounced in boys. Even at five months of age, a higher prevalence of both iron deficiency and anemia became evident in males as compared to female subjects. Of note, at this early stage, there was a negative association between higher hepcidin levels and gain of weight and length in both sexes, confirming that infection-driven elevation of hepcidin negatively impacts on iron absorption.[8]

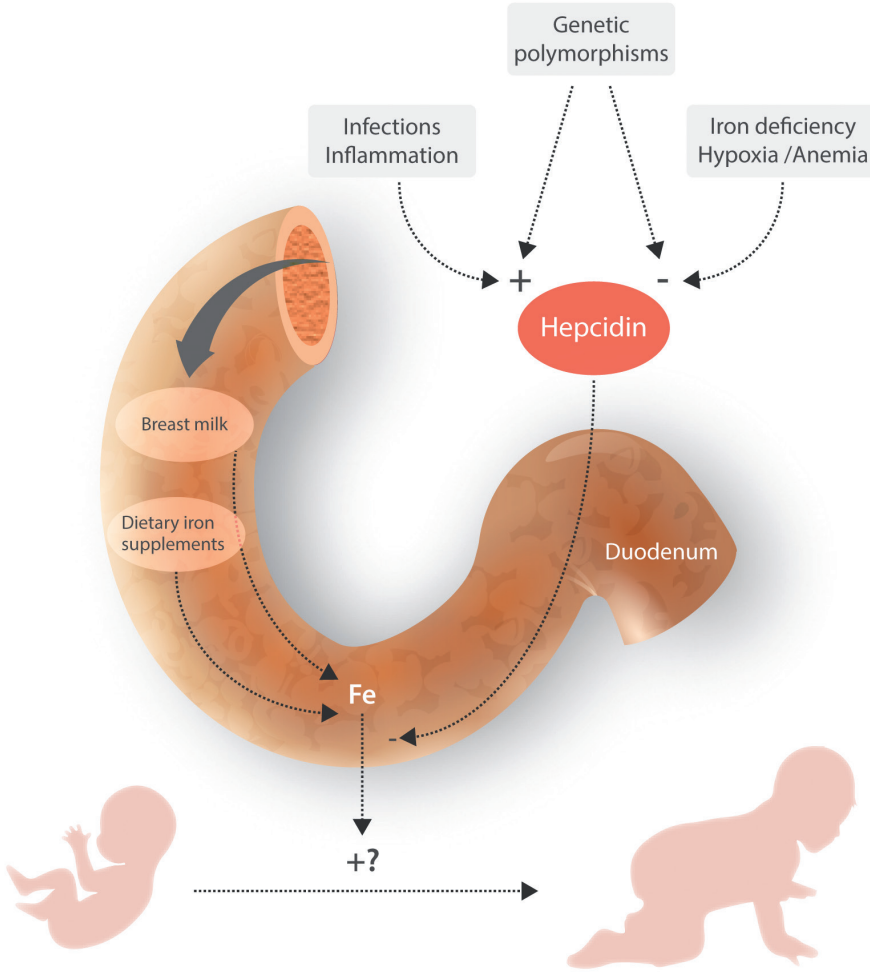

Figure 1. Factors impacting on iron availability and absorption for infants. Dietary iron is absorbed in the duodenum. The bioavailability and quantitative absorption of iron are dependent on the one hand by the molecular/heme iron content of the diet and on the other hand on the concentration of hepcidin. The latter blocks the transfer of iron from the duodenal enterocyte to the circulation, which is a prerequisite for iron availability for cells and tissues. Among other factors, hepcidin expression is stimulated by infection and inflammation, inhibited by iron deficiency, anemia and hypoxia, and can be influenced by genetic polymorphisms of iron metabolism genes in either direction. It is anticipated that efficient incorporation of the metal by infants is positively associated with promotion of growth and mental development.

Nonetheless, this leads to questions about the mechanisms underlying gender-specific differences in developmental growth and iron handling in infancy. Iron absorption and iron utilization for erythropoiesis are known to be affected by genetic polymorphisms in different iron metabolism and erythropoietic genes.[2,16] Apart from the description of sex-linked anemia in mice and males,[1] no specific genetic defects with higher prevalence in females have been described. One might also speculate that cultural differences in feeding procedures between boys and girls or dietary additives in addition to breast feeding which impact on iron bioavailability, may play a role in this setting. It could also be that there is a higher driving force of iron to be incorporated into muscle tissue in boys than in girls, although this would be surprising at this early stage of development. The latter is believed to be rather driven by sex-specific effects of hormones which would not be evident in infancy. Later on in life, this may become more relevant, because testosterone promotes muscular development whereas estrogens have a positive effect on inflammatory pathways which may negatively impact on dietary iron absorption.[7] The same also holds true for hormonal effects on hepcidin expression, which is reduced by testosterone but likewise only becomes important in adolescence. Differences in the prevalence of infections with associated impairment of dietary iron absorption also do not appear to account for this because fewer females than males were affected by infections. Another issue could arise from sex-specific differences in intestinal infestation with hookworms which aggravates iron losses by duodenal bleeding. Nonetheless, it is also plausible that more sustained growth is independent of iron absorption, meaning that iron deficiency is the consequence, and not the cause, of growth that is actually driven by other factors. Thus, the issue of sex-specific differences in iron handling and putative iron-mediated growth promotion remains a matter of speculation which should be addressed in future prospective trials.

Not surprisingly, the authors[15] also found that hepcidin levels are much affected by markers of inflammation, namely C-reactive protein (CRP), but also by seasonality, both of which point to a role for infections in their impact on hepcidin levels. This observation generates new knowledge which can help predict the optimal time frame for iron substitutions; this could include recommending those months with the lowest seasonal burden of infections as this would increase efficacy or iron absorption and reduce the risk of an increased incidence or unfavorable course of infections. Moreover, iron administration has been shown to be quite safe when preventive measures for reducing the burden of infectious diseases are undertaken. A recent

report demonstrated that the use of insecticide to impregnate bed nets and screening for parasites in blood reduced the malaria risk in children on iron supplementation.[17] Moreover, recent data demonstrate that iron deficiency negatively impacts on immunological responses to diphtheria vaccine leaving children insufficiently protected against such infections (*N Stoffel, Zurich, oral presentation, Bioiron Meeting 2019*). Thus, this study by Armitage[15] and co-workers is an important step forward to gain more insights into the relative contribution of different regulatory mechanisms on circulating biomarker concentrations such as hepcidin and how this impacts on predicting therapeutic efficacy and the risk:benefit ratio of iron supplementation in a primary care setting.

Future studies will have to clarify the optimal timing and dose of iron supplementation to children, whether or not a continuous administration *via* dietary iron fortification or a once daily or once every other day application is preferable.[18] It will also be necessary to identify those children who might be at risk of unwanted effects of iron supplementation mainly arising from an increased morbidity and mortality from infections. Finally, we await further information on the impact of iron supplementation on growth and mental development, functionality of the immune system, efficacy of preventive measures such as vaccination, and the consequences of iron-mediated alterations of the intestinal microbiota on children's health.

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The wolf of hypomethylating agent failure: what comes next?

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Myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) are clonal hematopoietic stem/progenitor cell (HSPC) disorders mainly affecting the elderly population.[1] Hypomethylating agents (HMA) like azacitidine and decitabine have become the standard of care in elderly patients with high-risk (HR) MDS or AML unfit for intensive treatment approaches. Until today, responses to HMA have occured in less than 50% of patients and are not durable, with only a few patients achieving long-lasting remissions.[2,3] Prognostic clinical markers, such as presence of peripheral blasts, high transfusion burden, and poor performance status, have been identified as indicators of a worse outcome of HMA-based therapy.[1,4] Moreover, responses to HMA are especially short-lived in patients with adverse risk cytogenetic abnormalities compared to those with normal karyotype.[1]

Craddock *et al.* evaluated the impact of mutational profile on clinical response to azacitidine by analyzing 250 patients with newly diagnosed, relapsed, or refractory AML or HR-MDS. Lower complete response (CR) rates occurred in patients with an IDH2 and STAG2 mutation, higher CR rates in patients with NPM1 mutation. Mutations in CDKN2A, IDH1, TP53, NPM1, and FLT3-ITD were associated with a worse overall survival (OS) in univariate analysis, while multivariate analysis showed a decrease in OS in patients with CDKN2A, IDH1, or TP53 mutations. Moreover, ASXL1 and ETV6 were associated with short response duration after azacitidine treatment.[5]

Despite all efforts to try to select patients based on