Hepcidin and the Global Burden of Iron Deficiency

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Iron deficiency anemia is the most common type of anemia worldwide. It primarily affects women and children and is particularly prevalent in regions where their diet contains little meat, malaria and intestinal parasites are common, women have many closely spaced pregnancies, and children suffer from diarrheal illnesses (1). Iron deficiency alone or in combination with other forms of malnutrition may impair cognitive development and decrease initiative and physical stamina. On the other hand, iron deficiency may be protective against malaria. Indiscriminate iron supplementation may increase the risk of mortality from malaria and other infections, by mechanisms that are not well understood.

Although the optimal strategy for iron supplementation in such settings is not yet established, it makes sense that iron supplementation should be directed only to those children who are known to be iron deficient, will absorb the supplemental iron, and will utilize it to increase their hemoglobin concentrations. Finding a simple, field-friendly diagnostic test that would sensitively and specifically identify children who are most likely to benefit from iron supplementation (and ideally also are least likely to be harmed) has become the Holy Grail of iron-related diagnostics in the global setting.

Pasricha et al. (2) have made an important advance in this quest by testing the ability of serum hepcidin measurements to identify iron deficiency in well-characterized blood sample collections from children in areas of the Gambia and Tanzania where malaria is endemic. In addition to conventional diagnostics (serum ferritin, soluble transferrin receptor, and soluble transferrin receptor/log serum ferritin) used to define iron deficiency in all children, a smaller group of children was tested for their ability to incorporate an orally administered stable natural isotope of iron (57Fe) into erythrocyte hemoglobin. Children who were iron deficient according to the conventional definitions also absorbed and used iron more efficiently than children who had other types of anemia. Although these measurements define a group of children who are most likely to benefit from iron supplementation, a simple test for iron deficiency is needed for these medically resource-poor settings.

Intestinal absorption of dietary iron and iron supplements is under the control of the iron-regulatory peptide hormone hepcidin and its receptor/iron transporter ferroportin (Fig. 1) (3). Ferroportin mediates the movement of dietary and supplemental iron from the small intestine to plasma and functions as a valve that regulates iron delivery to the erythropoietic bone marrow and other organs. Hepcidin controls iron flows by binding to ferroportin and causing its endocytosis and proteolysis, thus closing the valve. Hepcidin is secreted by hepatocytes at a rate that is stimulated by iron signals (both stores and plasma iron-transferrin concentration) but is suppressed by one or more substances secreted by erythroblasts in the marrow (erythropherrone and others). During iron deficiency, hepcidin often decreases below the limit of detection, allowing maximal iron absorption and release of iron from any remaining internal stores. After bleeding episodes, compensatory erythroid expansion signals through erythropherrone to suppress hepcidin and allow the absorption of more iron needed for the correction of anemia. This homeostatic system allows the maintenance of stable stores and plasma iron concentrations under various environmental stresses and facilitates the restoration of red blood cell mass after hemorrhage.

Hepcidin also functions as a mediator of host defense. During infections, under stimulation by cytokines (chiefly interleukin-6), hepcidin increases within hours and causes an acute decrease of plasma iron concentration. Lowered plasma and extracellular iron concentration presumably limits the supply of iron to microbial invaders. Prolonged increase in circulating hepcidin concentrations restricts the flow of iron to the bone marrow, limits erythropoiesis, and contributes to the characteristic anemia that develops during chronic infections and inflammatory disorders. Although anemia of inflammation (also called anemia of chronic disease) shares many features of iron deficiency anemia, anemia of inflammation is characterized by high hepcidin concentrations stimulated by inflammatory cytokines.

Because hepcidin controls the absorption of orally administered iron, low hepcidin should correlate with the ability of individuals to absorb iron. Because hepcidin synthesis is controlled by iron, low serum hepcidin concentrations should reflect iron deficiency, i.e., low or absent iron stores and low concentration of iron in plasma. Pasricha et al. now show that these physiologically based
In areas with high prevalence of malaria and limited diagnostic resources, it may be necessary to perform additional diagnostic studies in children with severe anemia to establish whether they are infected. In the setting where other causes of anemia as well as malaria and other infections are highly prevalent, it may be reasonable to treat severely anemic children with empiric antimalarials before administering iron.

Serum ferritin, another biomarker of iron deficiency, has a very different role in iron metabolism. It reflects the amount of iron in intracellular storage where iron is complexed within cytoplasmic ferritin. Because most iron is stored in macrophages and hepatocytes, serum ferritin is particularly responsive to processes that involve these cell types. Nevertheless, serum hepcidin and serum ferritin trend similarly under a variety of physiologic and pathologic conditions. The direct role of hepcidin in the regulation of intestinal iron absorption could make it a better predictor of the utilization of supplemental iron, but the relative performance of ferritin and hepcidin as clinical markers of iron deficiency and iron utilization needs to be determined in clinical trials.

Much remains to be done to implement these findings for the benefit of children in regions where iron-deficiency anemia is endemic but so are tropical infections and other causes of anemia. A field-friendly and sensitive hepcidin assay will have to be developed and validated under realistic conditions. The assay will then have to be tested for its ability to guide iron supplementation in a way that alters clinically meaningful outcomes, including improvements in cognitive development and general measures of physical health and fitness. Importantly, these improvements must occur without significant increases in morbidity and mortality from malaria and enteric infections.

**Fig. 1. Hormonal control of iron homeostasis by hepcidin.**
The major flows of iron into plasma and extracellular fluid are controlled by the effects of hepcidin on the iron exporter ferroportin (FPN). Hepcidin regulates the absorption of iron from the diet, including oral supplements. It also controls the release of stored iron in the liver and the release of iron recycled from senescent erythrocytes, mostly in the spleen.

**Expectations are fulfilled even in the complex setting of rural Gambia and Tanzania:** children with low serum hepcidins were highly likely to have iron deficiency and to absorb supplemental iron. The authors then went on to establish specific hepcidin cutoffs that efficiently predict iron deficiency and ability to absorb and utilize iron in the setting where other causes of anemia as well as malaria and other infections are highly prevalent.

Although low hepcidin may predict the ability to absorb iron in children with moderate anemia, other investigators have reported that very severe malarial anemia may suppress hepcidin to below detectable concentrations (4, 5). In these settings, very high erythropoietin concentrations may greatly increase the secretion of erythroferrone (6) and perhaps other hepcidin-suppressive erythrokines, so that low hepcidin no longer reports simple iron deficiency treatable with oral iron preparations. To avoid the potential risks of iron therapy in severely anemic children with malaria or other infections, it may be necessary to perform additional diagnostic studies in children with severe anemia to establish whether they are infected. In areas with high prevalence of malaria and limited diagnostic resources, it may be reasonable to treat severely anemic children with empiric antimalarials before administering iron.

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**References**


