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Iron Deficiency: A Concise Review

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Iron deficiency is a major worldwide health problem. There is recent evidence that the anemia is only the last manifestation of the syndrome and that symptoms occur before the anemia is manifest. Advances in outlining the physiology of iron deficiency have been made, gaps remain in the current understanding. While oral iron supplement remains the mainstay, some indications for the intravenous administration have developed. This review will highlight the epidemiology, physiology, clinical presentation, and treatment options. Am. J. Hematol. 78:225–231, 2005. © 2005 Wiley-Liss, Inc.

Key words: iron deficiency anemia; DMT-1; mobilferrin; hepcidin; hephaestin; ferroportin; iron sucrose

INTRODUCTION

The most common nutritional deficiency is the deficiency of iron. It has the highest prevalence in the US among women and young children. Women ages 16–19 have an iron deficiency incidence as high as 19%. Iron deficiency increases in minority populations and is as high as 22% in Hispanic women. In children of both sexes age 1–2 years, the prevalence is 7%. In infants and preschool children, iron deficiency anemia results in decreased motor activity, social inattention, and decreased social interaction [1]. These defects are persistent if not corrected [2]. Among pregnant women, iron deficiency anemia during the first two trimesters results in increased incidence of preterm labor and low-weight births [3]. The prevalence of anemia in low-income pregnant females in the 1st, 2nd, and 3rd trimesters is 9%, 14%, and 37%, respectively. Iron deficiency anemia results in (1) decreased work productivity (2) increased child mortality, (3) increased maternal mortality, (4) slowed child development, and (5) mild-to-moderate anemia may increase susceptibility to infectious disease [4].

Iron deficiency without overt anemia can result in neuropsychological effects and has been linked to delayed cognitive development in children and adolescents [5]. These delays may respond to iron therapy [6]. Non-anemia iron deficiency probably does reduce work capacity [7]. Tissue iron deficiency without anemia impairs endurance capacity after aerobic training in previously untrained women, which can be corrected with iron supplementation [8]. Therefore, anemia is only part of the overall syndrome of iron deficiency.

Diet predicts iron status into infancy and early childhood. Between 20% and 40% of infants fed cow's milk or nonfortified formula are at risk, as are 15–20% of breast-fed infants [9]. Breast milk has the greatest amount of bioavailable iron. Beyond the age of 24 months, the incidence of iron deficiency decreases with the decreased dependence on milk. In older children, the risk for deficiency is related to limited access to food because of family income, low-iron diets, or medical conditions such as bleeding or inflammatory disease. Iron requirements increase due to growth during adolescence (12–18 years). Among females, menstrual blood loss becomes an issue, and heavy loss (greater than 80 mL/month) is a significant risk factor. Other factors for this population include use of an intrauterine device, high parity, and low iron intake [10]. Among pregnant women, the expansion of the blood volume, growth of the fetus, and other maternal tissues increases the demand for iron 3-fold. In the absence of iron

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supplements, many pregnant women are unable to maintain iron stores, although prevalence data across the entire population are not available. While some iron is returned by contraction of the blood volume after delivery, the iron deposited in fetal and supportive tissues is lost from the mother. Data from HANES III indicated that 11% of nonpregnant women aged 16–49 have iron deficiency and 3–5% have iron deficiency anemia. Worldwide, the problem of anemia is magnified. As many as 49% of children under the age of 5 may be iron deficient, and probably 25% of adult females [11].

In the developing world, the effect of parasite infestation should never be underestimated [12]. Anemia can result from infections of *Trichuris* (whipworm), through intestinal loss [13]. Blood loss in children can be estimated to be about 0.005 mL/day/worm [14]. Because infestations of several thousand worms are not unusual, this can result in iron deficiency anemia. Even more significant is the chronic intestinal blood loss due to the feeding habits of hookworms. "Hookworm disease" is a synonym for iron deficiency anemia in much of the world [15]. In the developing world, 56% of pregnant women are likely anemic as are an amazing 74% of pregnant women in Southeast Asia. A large percent of these anemias are thought to be secondary to hookworm [16]. Current estimates indicate that from 30 to 44 million pregnant women also harbor hookworms (usually *Necator americanus*) and that perhaps over 7.5 million infected pregnant women live in sub-Saharan Africa. An average woman in sub-Saharan African 18–43 years of age spends as much as 28% of her time pregnant and 65% lactating. In India 20% of maternal deaths are due to anemia. In the Ivory Coast [17], Sri Lanka, and Sierra Leone, treatment for hookworm improved hemoglobin levels significantly [18,19]. A study involving 3595 children attributed 35% of cases of iron deficiency anemia and 73% of cases of severe iron deficiency anemia to hookworm infection [20]. Workers in the developing world doing physical labor (such as rubber, road, and sugar cane workers) become more productive if they are treated for hookworms and other infections, given iron supplements, and increased energy intakes [21,22]. Productivity loss in South Asia due to iron deficiency may amount to $5 billion dollars per year [23].

Dietary iron is present in two forms, as inorganic iron and heme iron. In meat, 50% of the iron is heme and 15–35% is bioavailable [24]. While most iron in the diet is inorganic iron, its absorption ranges from 2% to 20%, so that a large source of iron is from organic sources. In developed countries, perhaps two-thirds of the iron is derived from heme [25]. Nonheme iron absorption is facilitated by meat, ascorbic acid, but inhibited by phytates, some dietary fibers and lignins, phenolic polymers, and calcium. Unusual dietary habits resulting in the ingestion of chelators such as starch or clay are still found in clinical practice. Gastric acid is required in order to maintain the common ferric form of inorganic iron soluble, and achlorhydria may be a significant cause of iron deficiency in the elderly. Perhaps 30% of the elderly have achlorhydria [26]. Gastric atrophy and *Helicobacter pylori* gastric infestation may result in altered pH and iron deficiency [27]. Pharmacological iron is ferrous iron, and its absorption is not dependent on gastric pH so that treatment in achlorhydric individuals with oral supplements is effective.

Bleeding is the most common cause of iron deficiency, often associated with inadequate iron intake. True inability to absorb iron is extremely rare. Bleeding into the hip joint space or intra-abdominally may be initially undetected. Menstrual loss may not be reported as bleeding. A 1-mL loss of blood would translate to a loss of 0.5 mg of iron. Occult bleeding may be due to GI loss, but a loss of 20 mL/day is needed for the usual stool test to become positive for occult blood. Rarely may hemosiderinuria cause iron deficiency. Failure to absorb iron can occur in gastrointestinal disease with extremely high transient time, such as is seen in celiac disease. A recent cause of iron deficiency is the use of erythropoietin to treat chemotherapy induced a renal failure related anemia when iron was not administered concomitantly [28]. Anemia is common in intensive care units and is occasionally attributed to bleeding and blood draws for laboratory tests [29]. However, in most instances the ICU anemia is a form of "anemia of chronic disease" with diminished erythropoietin production, impaired proliferation, and altered iron metabolism, largely due to the systemic inflammatory response syndrome [30].

PHYSIOLOGY OF IRON

Iron is transported in the plasma bound to transferrin as diferric transferrin. There is a specific receptor on the cell surface, the transferrin receptor (TfR), with high affinity ($\sim 10^{-9}$ M dissociation constant), and the complex is internalized via a clathrin-coated pit. The pit fuses with an endosome that is then acidified, decreasing the affinity of transferrin for the iron and releasing it. The transferrin–TfR complex is then recycled to the cell surface, where it is externalized, and the apotransferrin is released. What happens to the iron within the cell is unknown. It may cross the endosome membrane by either of the pathways used in intestinal plasma membrane iron transport, but transport through the cytoplasm is not understood. There may be a direct contact between the endosome and the mitochondrion to transmit the iron [31].

During intrauterine life a fetus accumulates about 250 mg of iron from maternal sources. A newborn infant has about 80 mg/kg, which decreases in the first year of life to about 60 mg/kg. A growing child maintains this by absorbing about 0.5 mg of iron in excess of body losses to ultimately achieving 4,000 mg (70-kg man). The majority (two-thirds) is contained in hemoglobin, and about 1,000 mg is in ferritin or hemosiderin. A woman has a smaller body store of iron (about 3,000 mg) due to menstrual losses and childbirth. Men absorb and excrete about 1 mg of iron daily, and during their child-bearing years women must absorb twice as much.

Iron is absorbed through the intestine. At least three pathways have been described. Two pathways utilize iron as inorganic iron in the ferric valence (the mobilferrin, integrin, paraferritin [MIP]) or the ferrous valence (DMT-1) iron, and the third pathway uses organic iron from heme. Almost nothing is known about the mechanism of heme iron absorption, except that the porphyrin is cleaved by endogenous hemoxygenase. The DMT-1 protein is a classic transmembrane pump, increased in iron deficiency, and decreased in the Belgrade rat and mk mouse, both noted for microcytic anemia and systemic iron deficiency. It was assumed that this mutation was "leaky" because the animals were alive, but the nonleaky equivalent mutation in zebrafish is also alive, which implies that the DMT-1 pathway cannot be the sole pathway [32]. There are data to suggest that the Belgrade rat defect is not at the intestinal membrane but further into the iron transport sequence, perhaps at the endosomal stage [33]. The DMT-1 protein transports a number of divalent metals in model systems, including ferrous, but not ferric, iron. Because the duodenal iron is likely ferric, the ferric iron in the diet would need reduction to ferrous iron prior to transport by DMT-1, and this may be accomplished by a membrane cytochrome containing ferrireductase (converting ferric iron, Fe(III), to ferrous iron, Fe(II)). This enzyme is increased in iron deficiency, but it has not been shown to have a direct role in transport. The reduction would require a source of reducing power, which has not been identified but could be ascorbic acid in rodents (but presumably not in scorbutic animals like man). It is not known if the reductant needs to be on the lumenal side of the plasma membrane or if only the electron crosses the membrane. The MIP pathway involves a complex series of nonclassical proteins, including a protein mobilferrin, which is highly homologous to a chaperone protein calreticulin [34]. Mutations in this protein are lethal, but this may not be due to the iron transport function, because calreticulin is involved in a variety of cellular processes. In tissue culture, these two pathways are independent. Ferric iron would not require reduction to be transported but would require reduction to ferrous iron to serve as a substrate for ferrochelatase. This may be accomplished by a ferrireductase found in a large protein complex called paraferritin.

The cellular localization of the transmembrane transport proteins is not straightforward. This is due in part to their involvement in the transport of iron out of the endosome, and endosomal location is evident. Under normal conditions DMT-1 is largely found in the cytoplasm and lamina propria, but is brought to the lumenal surface in iron deficiency. The mutation in the mk mouse results in defective transport to the apical membrane [35]. In iron deficiency, DMT-1 is localized in the apical membrane, but on refeeding with iron, it internalizes as vesicles. Whether this is due to a regulation by internalizing the transporter [36] or a mechanism for transport itself is not completely clear, but co-localization of apotransferrin and DMT-1 was observed in endosomes in cultured cells, suggesting a "transcytosis" [37]. Mobilferrin is likewise found in the cytoplasm and the cell surface. During iron deficiency, mobilferrin does not quantitatively increase but becomes localized at the cell membrane. In the case of both DMT-1 and mobilferrin, electron microscopy revealed that the majority of the apical surface increase in the amount of these proteins was due to increased binding of the proteins to mucin in vesicles near the lumenal surface. Significant amounts of the proteins were found outside the cell in the lumen, attached to mucin, and only trace amounts were found on the membrane itself. This suggested that the transport proteins might scavenge metals in the lumenal space and return to the membrane along a mucin track [38]. Vesicular uptake by DMT-1, or a large molecular weight complex for mobilferrin, would appear to be a more reasonable part of this mechanism than a simple ion pump function.

Once across the lumenal membrane of the duodenum, the iron must exit as transferrin. The iron needs to transit the cytoplasm, and this probably involves a carrier protein. If the intracellular form is ferrous, the likelihood of generating free radical damage and cell death is sufficiently high to make it likely that the iron must be confined in some manner. If the iron is in the ferric form, the risk of free radical damage is decreased, but it must be chelated to be soluble. Once at the basolateral membrane, the iron will be incorporated into transferrin in order to be released to the plasma. There must be an independent apo-transferrin receptor on the basal–lateral side of the intestinal cell, although this has not been shown. The usual transferrin receptor, which is present on the basolateral membrane, will be saturated with diferric transferrin and unavailable for apo-transferrin.

Hephaestin, a ceruloplasm-like ferro-oxidase, and a transport protein ferroportin appear involved in the

exodus of iron from the intestinal mucosa [39]. Hephastin is a multicopper enzyme that can oxidize ferrous(II) to ferric(III) for incorporation into transferrin that binds only the ferric form. In mice, a mutation in hephastin (the sex-linked anemia) cannot release iron across the basolateral membrane. Another protein, ferroportin [40], appears to be the actual transmembrane transporter. Hephaestin and ferroportin appear to respond to systemic rather than local (i.e., duodenal) iron levels and may exercise control of iron uptake at that stage [41].

The mechanism by which the cell detects the body stores of iron is not known. Because the concentration of diferric transferrin in the blood is about 3 micromolar, and severe iron deficiency drops this by two-thirds, the remaining levels are sufficient to completely saturate the transferrin receptor. Some alternative method of sensing the plasma iron concentration must occur, but it is not known [42].

Hepcidin may be a major communicator between iron stores [43] and the intestinal absorption mechanism [44]. Hepcidin is increased in the liver of iron-overloaded mice [45]. The liver may detect changes in the diferric levels by the ratio of transferrin to receptors, and as these decrease, hepcidin levels are also reduced. Circulating hepcidin alters ferroportin levels in the villi, controlling intestinal iron uptake [46]. Hepcidin reduces the expression of the iron transporter DMT-1 [47]. Hepcidin administered to mice significantly reduced mucosal iron uptake and transfer, and carcass examination showed that at least 10 μg/mouse/day had been transferred [48]. Hepcidin is downregulated in hypoxia and may explain the increase in iron absorption under hypoxia and the increased iron release from reticuloendothelial cells. Chronic inflammatory models (turpentine injection) in mice result in a pattern similar to anemia of chronic disease [49], and increased urinary excretion of hepcidin is observed in humans with anemia of chronic disease [50]. These data have suggested that hepcidin is the regulator in anemia of chronic disease [51]. This response to inflammation may be mediated by interleukin-6.

How iron deficiency directly affects the cell is largely unknown. In iron deficiency there is an increase in red cell free porphyrin, so presumably the enzyme that places the iron in the heme, ferrochelatase, is inhibited. Hemoglobin protein synthesis is probably also inhibited, but possibly there is some residue chain initiation [52]. Ribonucleotide reductase (RR) is a non-heme iron protein that is commonly stated to be the enzyme most sensitive to iron deficiency, and inhibition by lack of iron is reported to stop DNA synthesis [53]. The inhibition of RR by hydroxyurea results in macrocytic (DNA synthesis inhibition), not microcytic (iron deficiency), anemia. Loss of RR by iron chelation occurs within 4 hr in culture, which qualifies it as an "early" event [54]. In a transferrin transport defective cell line, presumably intracellularly iron deficient, there was a decrease in RR activity, but not protein synthesis, as its major defect [55]. Other essential heme proteins might be involved, in particular those of the respiratory chain in the genesis of loss of energy and CNS function. Severely anemic rats with 50% decrease in hemoglobin have an almost 50% reduction in myoglobin and cytochrome *c* [56] and decreases in iron–sulfur content, pyruvate dehydrogenase, and other tricarboxylic acid (TCA) cycle enzymes. Perinatal iron deficiency in rats decreases cytochrome *c* oxidase activity in the neonatal brain [57]. In contrast, in milder anemia, with hemoglobin levels in the range of 6–12 g/dL, there was an increased platelet count, increased serum transaminase consistent with cell damage but no decrease in the activities of TCA enzymes or cytochrome oxidase activity [58]. The naïve explanation for the lack of energy does not appear to be correct. Abnormalities in lipid composition were observed, consistent with effects on lipid desaturase activities [59]. The physiology of iron deficiency is still under-explored.

A variety of genes are increased in iron deficiency as observed in limited DNA microarray data, including Rb, p21, cdk2, cyclins A, D3, E1, myc, iNOS, FasL, none of which is intuitively related to iron metabolism but which may help account for the signs and symptoms. Many of the proteins involved in iron homeostasis may be regulated at the translational (rather than transcriptional) level. The mRNAs of ferritin, transferrin receptor, aminolevulinic acid synthetase, ferroportin, m-aconitase, and DMT-1 are regulated by an iron-responsive element (IRE) on the mRNA, which binds either of two binding proteins to regulate translation.

SIGNS AND SYMPTOMS

Individuals with iron deficiency may experience no symptoms. Findings common to all anemias may be present, or those rather specific to iron effects on rapidly turning over epithelial cells resulting in glossitis, gastric atrophy, stomatitis, ice eating (pagophagia), and leg cramping. The esophageal web syndrome (Plummer-Vinson syndrome) is still reported to be related to iron deficiency, and at least some cases appear to respond to iron therapy [60]. Koilonychia or spoon nails may more commonly be due to fungal infections or hereditary variations [61].

Definitive diagnosis requires laboratory tests [62]. A bone marrow smear containing no stainable iron is definitive. Elevated total iron-binding capacity, low serum iron level, and a low serum ferritin concentration are considered diagnostic for iron deficiency.

Transferrin saturation should be less than 10%. However, serum iron is subject to diurnal variations, with higher concentrations late in the day, and may be increased after meat ingestion. Oral contraceptives increase serum transferrin and result in low transferrin saturation. The serum ferritin reflects body stores and is not affected by recent iron ingestion. Ferritin is an "acute phase reactant" and in the presence of infection or inflammation the ferritin may be high and the serum iron and transferrin low. Perhaps a better estimate of body stores is obtained by the ratio of serum transferrin receptor (sTfR) to serum ferritin (R/F ratio) [63,64]. Studies of the R/F ratio shows age dependence [65]; in males there is a Gaussian distribution, but in females there is a bimodal distribution. The R/F ratio can also be affected by inflammation. However, at least in the elderly, the R/F ratio may be more sensitive than the classic blood tests [66] and may be more sensitive in distinguishing iron deficiency anemia from the anemia of chronic disease [67]. A major problem is the lack of standardization of the sTfR assay. There has been interest in using erythrocyte zinc porphyrin as an assay [68]. This may be useful in primary screening tests for assessing iron status. It is likely due to the increase transport of Zn across the intestine by the upregulation of the DMT-1 in iron deficiency.

In individuals treated with recombinant erythropoietin, the increased production of RBCs exhausts iron stores rapidly, resulting in serum iron being reduced and transferrin becoming desaturated. In healthy individuals iron stores determine the response to erythropoietin, and baseline ferritin values $< 1{,}000$ μg/L have been associated with a "functional" iron deficiency. Ferritin concentrations are not correlated to body stores in the setting of hyperthyroidism, malignancy, inflammation, hepatocellular disease, alcohol consumption, and oral contraception use. The percentage of hypochromic RBC and hypochromic reticulocytes may or may not be useful in identifying functional iron deficiency and in predicting response to erythropoietin and i.v. iron treatments. This percentage is not useful in the settings of thalassemia or chemotherapy patients [69].

TREATMENT

The preferred treatment, besides identification of the source of iron loss, is oral iron. Ferrous iron salts are preferred because of their increased solubility and availability at the pH of the duodenum and jejunum. Standard therapy for iron deficiency anemia in adults is oral administration of a 300-mg tablet of ferrous sulfate (60 mg of elemental iron) three or four times daily. While absorption is enhanced by administration of the iron on an empty stomach, epigastric pain develops in some patients if iron is administered in the fasted state, so it must be taken with meals. In addition, heartburn, nausea, vomiting, and diarrhea may occur. These symptoms can be reduced by administering the tablets with meals, decreasing the dose of iron, by switching from ferrous sulfate tablets to other preparations containing less iron, such as ferrous gluconate tablets (320 mg with 36 mg of elemental iron), or by the oral administration of carbonyl iron (Ircon). Pediatric liquid preparations of iron (Fer-In-Sol) can be used with dose modifications to avoid side effects. In order to ensure a response to treatment, the anemia should be monitored. The usual cause of failure to respond is noncompliance, but failure to absorb enteric-coated iron tablets or malabsorption of iron due to high transit times may occur. True malabsorption of ferrous sulfate is extremely rare, but it may be diagnosed by administering an oral dose of liquid ferrous sulfate (50–60 mg of iron) in a fasted state and obtaining a serum iron level before administration and 1 and 2 hr later. An increase in the serum iron concentration of 100 μg/100 mL should be observed.

Reticulocytosis may be observed as early as 4 days after treatment and will reach a maximum at 7–10 days. An increase in the hematocrit and hemoglobin concentration will follow. Therapy needs to continue for 2–3 months after correction of the anemia in order to replenish the body stores of iron.

Iron for intramuscular or intravenous administration was available in the form of iron dextran (INnFeD), but it had a high toxicity rate and is now rarely indicated. In contrast, iron sucrose appears safer. The iron is delivered to endogenous iron-binding proteins with a half-life of 90 min. It becomes rapidly available for erythropoiesis. Some formulations such as Venofer® can cause anaphylactoid reactions. Other parenteral preparations, such as ferric gluconate and ferric citrate, deliver iron to many proteins other than iron-binding proteins and can be deposited in the parenchyma of the liver, resulting in necrosis [70]. Oral iron products have been largely abandoned in patients with end-stage renal disease, most of whom are being treated with erythropoietin. Parenteral iron can be administered by slow intravenous injection, intravenous drip infusion, or injection into the dialyzer. The most frequent adverse effects reported during treatment in hemodialysis patients are hypotension, cramps, and nausea. Some dialysis centers have tried oral heme iron [71]. Some authorities are recommending the combination of erythropoietin and intravenous iron (iron sucrose 200 mg i.v. and rhEPO 300 U/kg twice a week) for rapid reversal of anemia in pregnant patients [72].

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