Understanding Iron Absorption and Metabolism, Aided by Studies of Hemochromatosis*

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ABSTRACT

Duodenal iron absorption from food is selectively blocked to prevent iron intoxication. The prime example of pathologic increase in intestinal iron absorption is seen in patients with hemochromatosis. They suffer iron damage to the heart, liver, and other tissues resulting in premature death if the iron is not removed by vigorous phlebotomy. Examples of overcoming the intestinal barrier to iron are alcohol consumption, vitamin preparations with vitamin C, and iron consumed by individuals without anemia. Endogenous generation of excess iron by hemolysis, owing to abnormal hemoglobin or many transfusions, are not controlled by the intestinal barrier.

Introduction

Iron is highly toxic but essential to the human organism. Food may contain abundant inorganic iron. Cereal, as example, may have 1 to 166 mg of iron per serving. The acid pH in the stomach facilitates solubilizing the iron but does not induce absorption. To overcome the increasing pH of the small intestine, iron is combined with gastric mucin. Integrin on the duodenal cell surface facilitates iron transfer into the cytoplasm, where it is bound by mobilferritin. The final mobilferritin-iron-flavinmonooxygenase complex assures that iron is maintained in the appropriate redox state.1,2,3,4

Cells containing excess iron stimulate the synthesis of ferritin, the protein which incorporates iron to prevent oxidative cell damage.5,6 Cellular transferrin receptors permit transfer into the cell as well as from cells into the plasma.4 The normal adult iron requirement is 1 to 2 mg per day and is readily available in a "healthy diet." If excess iron is ingested but not absorbed, normal iron stores are the result. The most common absorption problem results from absence of gastric acid secretion in patients following gastric resection or with gastric mucosal atrophy; no iron is rendered absorbable and all dietary iron is excreted. Adding acidification alone does not significantly increase the iron absorption. If mucin is decreased or absent as in atrophic gastritis, iron is not absorbed.

Blood loss owing to bleeding, exceeding the normal intestinal ability to absorb sufficient iron to replace the lost hemoglobin, is the most common cause leading to iron deficiency anemia in the male and postmenopausal female. Menstrual blood loss and pregnancy are the most common causes for iron deficiency in
females of childbearing age. These clinical examples are well known to the practicing physician causing iron deficiency anemia.

In 1972, Finch and Monsen predicted that the high incident of iron deficiency encountered in infants and the female population would be abolished by mandated iron fortification of food. Consequently, today iron deficiency anemia of childhood is rarely encountered. A recent survey found the range to be from <1 percent ages 3 to 11 years and 3 percent ages 1 to 2 years. During normal hemoglobin synthesis of new red blood cells, iron needed for hemoglobin replacement is provided by the destruction of the senescent red cells hemoglobin iron balancing the iron metabolism. Excess iron, however, accumulates in patients with abnormal hemoglobin containing red cells which are prematurely destroyed. Well known examples are hemolytic anemia owing to thalassemia or sickle cell anemia. Depending on the rate of destruction iron overload ensues, depositing the excess in the reticulo-endothelial system is the common cause of hemosiderosis in these children.

In the adult, 75 percent of the body iron is contained in the oxygen transport hemoproteins hemoglobin and myoglobin. Storage (ferritin) and transport (transferrin) proteins contribute only 13 percent of total body iron. Essential enzymes, cytochrome, peroxidase and catalase, contribute very little to the total body iron.

Progressive iron loading, resulting from an inborn error of metabolism was proposed as early as 1935 by Sheldon. The hereditary hemochromatosis locus has been linked to the HLA-A class I region of the human major histocompatibility complex, located on the short arm of chromosome 6. The HLA haplotype A3, B7, commonly seen in hemochromatosis patients, strongly supports a founder chromosome. Finally in 1996 two mutations in the HLA-H gene have been reported on chromosome 6, by Feder et al. identifying the autosomal recessive disorder of hemochromatosis.

There is a substitution of cysteine for tyrosine at amino acid 282 (C282Y, nucleotide 845) and of histidine for aspartate at amino acid 63 (H63D, nucleotide 187). Recent global testing confirms that the disorder is most common among northern European populations estimated at a frequency of 1/300, thus making it the most frequent inherited disorder. The large number of regions surveyed by Merryweather-Clarke demonstrates the global prevalence of these mutations.

Tests

Since progressive excess iron loading fails to produce clinical symptoms during the early stages, the appearance of symptoms suggest the iron overload has already caused tissue damage, most common in the heart and liver. Because liver biopsy for iron analysis has become a popular approach to diagnose hemochromatosis. Dry liver tissue is assayed for iron and the result is divided by the patients age. This result is used as the Iron Index (HII). If the result is equal to 1.9 or greater, the patient is classified as having hemochromatosis.

Caution in using HII is recommended by the study of Deugnier and his colleagues in France. Patients with end-stage liver cirrhosis were evaluated for the mechanism of iron loading in the liver. The study questions the reliability of the HII to establish the diagnosis of hemochromatosis. Only 36 percent of the study patients with hemochromatosis demonstrated an HII greater than the 1.9 result for the diagnosis of hemochromatosis. The remaining patients with the same index were shown not to have the disease, suggesting the HII overdiagnoses iron loaded patients as having hemochromatosis. The finding of diffuse iron overload common in patients infected with the hepatitis C and B virus and chronic alcohol ingestion highlights the difficulties depending on the HII to classify the cause as abnormal intestinal iron absorption from hereditary hemochromatosis.

The most helpful laboratory testing includes: serum iron, iron binding capacity, and ferritin.
Serum iron may range from 2 μg/dl to over 1800 μg/dl in the child having ingested its mother’s iron medication. Even in the adult, serum iron levels are influenced by the presence of iron in the food ingested, resulting in a wide fluctuation unless the individual has been fasting 8 hours. The iron blood level does not assess body iron stores. Serum iron levels are lowest during sleep or during fasting. Serum ferritin, however, ranging from 5 μg/L to >2000 μg/L, reflects the stored amount of iron in the body.20,21

The dilemma presented by the African sid-erosis owing to the absence of the European HLA patterns, demonstrates the value of using the transferrin saturation. Values >55 percent are associated with a high serum ferritin, with the mean of 2,132 μg/L versus the control transferrin saturation <55 percent and a ferritin of 841 μg/L or less, indicating secondary iron overload.22

Since phlebotomy is the most successful therapeutic modality to remove the excess iron, it is essential to utilize dependable serum ferritin values to assure that the iron is removed to a safe level about 15 to 30 μg/dl.

Gilcher, at the Oklahoma Blood Institute,23 has used ferritin testing successfully to calculate the available storage iron in his autologous blood donation program. Since 1 μg of ferritin is equivalent to 10 mg of iron and 1 mg of iron is needed for 1 ml of red blood cells, using the plasma volume times the ferritin concentration permits calculation of the volume of red cells that can be removed, to achieve a safe ferritin level of 15 to 35 μg/dl. Calculating the iron removed by phlebotomy serves as a cross check on the patients’ iron balance. This approach has been used by the authors in calculating the success of phlebotomy in patients with hemochromatosis (figure 1). A thorough evaluation can now be done without using radioactive labeled iron.

The highest ferritin level of 9,000 μg/L has been encountered in a patient who already had liver cirrhosis and liver cancer. Both sons of

![Graph](image-url)
the patient had high ferritin levels; the HLA typing confirmed one homozygous and one heterozygous hemochromatosis pattern.

The design of an acceptable program to remove excess body iron stores should not depend only on removing red cells by phlebotomy. Controlling the amount of iron ingested in the diet reduces the number of phlebotomies required to keep patients from iron loading. Antacids administered as calcium carbonate effectively prevented 45 percent of the administered iron from being absorbed in the study by O'Neil-Cutting and Crosby. Less effective were sodium bicarbonate or Mylanta II. The same study tested iron absorption, administering antacids with vitamins, especially vitamin C, to enhance iron absorption. Calcium carbonate decreased iron absorption by 13 percent but less than without the vitamin being added.

Summary

The large number of individuals with hemochromatosis have stimulated advances in understanding iron absorption. Having instituted a program for over 200 patients to be de-ironed by phlebotomy, the current authors confirmed that a decrease of ferritin to 35 µg/L assures removal of body iron stores. The recent demonstration of a hemochromatosis gene can be helpful in identifying family members with the disease.

References