Special article
Rev Hematol Mex. 2018 April-June;19(2):73-76.

Revista de Hematología

Disorders of iron metabolism: Too little, too much, too late.*

Trastornos del metabolismo del hierro: muy poco, demasiado, demasiado tarde

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Abstract

Elemental iron is essential for life and the biochemistry and physiology of iron balance and metabolism are now understood at the molecular level. Although iron deficiency remains a worldwide problem due to nutritional inadequacy, malabsorption, and blood loss, iron is often easily replaced. On the opposite end of the spectrum, mutations in genes responsible for normal iron hemostasis can result in hereditary hemochromatosis, a disease of iron overload. In this paper, the molecular biology of iron will be discussed in the context of human disease.

KEYWORDS: Iron; Hepcidin; Iron deficiency; Iron overload; Hemochromatosis

Resumen

El hierro elemental es esencial para la vida, y la bioquímica y fisiología del equilibrio del hierro y el metabolismo ahora se entienden desde el punto de vista molecular. Aunque la deficiencia de hierro sigue siendo un problema mundial debido a deficiencias nutricionales, malabsorción y pérdida sanguínea, el hierro es con frecuencia fácilmente reemplazado. Por otro lado, las mutaciones en genes responsables de la hemostasia normal del hierro pueden resultar en hemocromatosis hereditaria, enfermedad de sobrecarga de hierro. En este artículo la biología molecular del hierro se discutirá en el contexto de enfermedad humana.

PALABRAS CLAVE: Hierro; hepcidina; deficiencia de hierro; sobrecarga de hierro; hemocromatosis.

* Presented at LIX National Congress of Hematology, 25-29 April, 2018. Nuevo Vallarta, Mexico.

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Received: 5 April 2018

Accepted: 9 April 2018

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This article must be quoted
Kahn MJ. Disorders of iron metabolism: Too little, too much, too late. Hematol Méx. 2018 April-June;19(2):73-76.

BACKGROUND

Iron is a critical human element that is necessary for oxygen transport in the blood, needed for muscle metabolism, required for energy production, and important for proper immune function. The majority of the body's iron is found in the circulating red cell mass, although iron is also found in the erythroid marrow, muscle, and reticuloendothelial macrophages. The absorption of iron from the digestive track is highly regulated as iron is an essential element, yet humans have a limited ability to eliminate iron aside from gastrointestinal cell turnover and blood loss. Dietary iron is obtained mostly from heme-based sources such as red meats, but soybeans, lentils, tofu, cereals and spinach are sources of non-heme iron. In contrast to heme-based iron, non-heme iron is absorbed less well because iron contained in vegetables and grains is often chelated to oxalates and phytates which limit bioavailability.[1]

The critical peptide responsible for iron absorption is hepcidin, a 25-amino acid peptide produced by the liver.[2] Hepcidin controls iron entry into plasma via the enteric basilar membrane protein ferroportin. Ferroportin allows for iron entry into the blood stream and allows for scavenged iron following erythrocyte turnover to be released from macrophages. Hepcidin causes internalization and proteolysis of ferroportin, which inhibits iron absorption from the gut and inhibits iron release from macrophages. As such, elevated hepcidin levels are associated with decreased iron absorption and decreased iron release by macrophages in the reticulendothelial system. Hepcidin synthesis is regulated by four pathways: *1)* Iron regulation where high transferrin saturation leads to increased hepcidin production; *2)* Erythroid regulation where anemia leads to decreased hepcidin; *3)* Inflammatory regulation where elevated IL-6 leads to increased hepcidin, and *4)* Hypoxic regulation where hypoxia leads to decreased hepcidin. All of these pathways work to increase iron absorption when iron is needed (anemia, hypoxia, etc.) and to decrease iron when iron is unnecessary or potentially harmful.

In addition to the regulation of iron absorption by hepcidin, iron homeostasis is regulated at the cellular level. This is primarily accomplished through the regulation of the transcription and translation of two proteins, ferritin and transferrin.[3] Ferritin is the major iron storage molecule and transferrin allows for the transport of iron from the gut to the marrow, muscle, reticuloendothelial system and hepatocyte. The system works such that when cells are deficient in iron, ferritin translation is repressed and transferrin translation is augmented. The opposite occurs when the cell is iron replete; ferritin translation is augmented and transferrin translation is repressed. This is accomplished through binding of iron response proteins (IRPs), which act as transcription factors to iron response elements (IREs) found in the nuclear DNA. In the case of ferritin, a single 5′ IRE is found, and in the case of transferrin five 3′ IREs are found. Binding of IRPs to the 5′ IRE in ferritin inhibits transcription, whereas binding if IRPs to the 3′ IREs in transferrin stabilizes the mRNA. Iron deficiency allows for the binding of IRPs to IREs. As such, when cells are iron deficient, ferritin translation is repressed by transcriptional inhibition, whereas transferrin translation is augmented via the stabilization of mRNA. When the cell is iron replete, IRPs do not bind to IREs. As a result, ferritin translation is augmented due to absence of transcriptional inhibition, and transferrin translation is repressed due to a less stable mRNA. This elegant biochemistry helps to regulate iron balance at the cellular level.

Iron deficiency

Iron deficient patients present with a myriad of symptoms including fatigue, lack of sense of well-being, headache, difficulty concentrating,

and craving for ice or starch (pica). Most iron deficient patients are best treated with supplemental oral iron. Traditionally, iron replacement is recommended as oral ferrous sulfate 325 mg three times daily. Recent data suggests that this may be incorrect. A study looking at hepcidin levels with iron replacement found that iron administration as multiple daily doses, actually decreased absorption due to elevation in hepcidin levels.[4] The study suggested, based on ferrokinetics, that a single dose every other day may be the preferred method of iron replacement. A follow up study in iron deficient women found that there was increased fractional and total iron absorption with alternate day oral dosing when compared with daily dosing.[5] Not surprisingly, this study also found higher hepcidin levels with daily as compared with alternate day dosing. Based on these studies, alternate day dosing of ferrous sulfate should be preferred over the traditional thrice-daily regimen. Additionally, because oral iron replacement is fraught with side effects including constipation and gastrointestinal upset, alternate day dosing should be preferred as it is much better tolerated.

Occasionally, it is not clear whether patients are compliant with oral iron therapy or if they are not absorbing oral iron. A potentially useful and inexpensive test that seems to have been forgotten is the oral iron challenge test.[6] For this test, the serum iron is checked followed by ingestion of a single 325 mg iron sulfate tablet. One hour later, the serum iron is repeated. If absorption is normal, serum iron should increase by 100 mcg/dL.

For patients unable to absorb oral iron, particularly those with inflammatory bowel disease who not only lose blood but also have very high hepcidin levels due to inflammation, parenteral iron is necessary.[7] Although there have been many complicated formulas for calculating iron deficit, a very simple formula can be used that is simplified due to cancellation of units:

Iron deficit (mg) = Weight (lb) x (hgb desired – actual hgb).

To this, 600 mg are added for women and 1000 mg added for men to replace iron stores. Parenteral iron is available in several preparations including iron dextran, iron gluconate, iron sucrose, ferumoxytol and ferric carboxymaltose. Iron dextran, the oldest of these, has a 1% risk of anaphylaxis and has more limited bioavailability than the newer preparations. For this reason, the newer preparations are often preferable.[8] The newer preparations differ in dosing frequency and infusion duration but are otherwise interchangeable.

Hepcidin production is regulated upstream by bone morphogenic protein/SMAD, which in turn is regulated by a cluster of proteins including hemojuvelin, HFE, transferrin receptor 1 and 2, and matriptase-2 (TMPRSS6). When the protein cluster is intact, hepcidin production is responsive to normal regulation. Matriptase-2 is able to cleave hemojuvelin from the protein cluster. As such, activation of matriptase-2 leads to decreased hepcidin synthesis, which in turn increases iron absorption. A rare cause of anemia, iron refractory iron deficiency anemia (IRIDA), is characterized by profound anemia that does not respond to oral iron in spite of often undetectable iron levels. IRIDA is caused by mutations in matriptase-2 which allows for unencumbered hepcidin synthesis and resulting inhibition of iron absorption.[9] These patients require infusion of parenteral iron on a regular basis to preserve erythropoiesis.

Iron overload

Hereditary hemochromatosis (HH) is classically characterized by iron overload that produces skin bronzing, hepatic failure, cardiac failure and endocrine failure and was described as early as the 19th century. HH is best screened for by

an elevated transferrin saturation of over 45%. Increased hepatic iron can be detected with liver biopsy or with specialized magnetic resonance imaging for T2*. The most commonly associated mutations in patients with HH are in the HFE gene, part of the upstream regulatory complex for hepcidin.[10] Although mutations in HFE were described in 1996, the mechanism by which these mutations caused iron overload were unknown for several years as original investigations focused on potential HFE interactions in the gut. It is now known that HFE does not directly interact with the gut to affect iron absorption, but rather regulates hepcidin which directly interacts with ferroportin in the enterocyte. HFE is a class 1-like membrane associated protein that associates with transferrin receptors 1 and 2, hemojuvelin and others to regulate hepcidin synthesis. Two important mutations in HFE are responsible for the majority of cases of HH. Between 60 and 90% of patients with HH are homozygous for the C282Y HFE mutation. Up to 4% of patients with HH are homozygous for the HFE H63D mutation. Up to 10% of patients are compound heterozygotes for both HFE C282Y and H63D. Heterozygotes are only rarely affected with iron overload and its consequences. About 30% of patients with HH have mutations in other genes including hemojuvelin, ferroportin, hepcidin or transferrin receptor. Especially in the case of mutations in hemojuvelin, affected patients present at a much younger age with stigmata of iron overload than those with HFE mutations. HH is treated with phlebotomy. In contrast, patients with secondary iron overload, hemosiderosis, are most often treated with iron chelators.

Understanding the biochemistry of iron absorption has led to the development of novel therapeutics. Examples include the development of mini hepcidins and matriptase-2 inhibitors to treat iron overload.[11]

Because iron is essential for life, living creatures have evolved complex methods to regulate its absorption and metabolism. In the future, knowledge of these processes will allow us to develop novel therapeutics useful in the care of patients with iron related disorders.

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