The Pathophysiology of Transfusional Iron Overload

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KEYWORDS

• Iron overload • Pathophysiology • Mechanism • Thalassemia • Sickle cell disease • Blood transfusion • NTBI • Extra-hepatic iron distribution

KEY POINTS

- The pathophysiologic consequences of transfusional iron overload (TIO) are best understood in thalassemia major (TM) and broadly reflect the distribution of excess storage iron to heart, endocrine tissues, and liver.
- The pattern of excess iron distribution reflects the pattern of nontransferrin-bound iron (NTBI) uptake to these tissues.
- Storage iron does not directly damage cells but its intracellular turnover contributes to labile intracellular iron pools that generate harmful free radicals.
- TIO also increases the risk of infection due to increased availability of labile iron to microorganisms.
- In other conditions such as sickle cell disease, Diamond-Blackfan anemia, and myelodysplastic syndrome, the propensity to the extrahepatic iron distribution and its consequences vary compared with TM.
- The mechanisms underlining this variability may reflect differences in the transfusional iron loading rates, age of commencing transfusion, as well as differences between transferrin iron utilization and NTBI generation.

IRON HOMEOSTATIC MECHANISMS

Iron homeostatic mechanisms are key to the pathophysiology of transfusional iron overload (TIO). In humans, these mechanisms are best adapted to increasing iron acquisition in conditions of iron deficiency or anemia, or to limiting iron distribution from the macrophage system during inflammation. They are not well adapted, however, to controlling the distribution of TIO or to eliminating excess iron. This is in

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marked contrast to rodents, where most studies on iron overload and iron metabolism have been performed and where iron overload is eliminated efficiently by the biliary route. Iron homeostasis is adapted to supplying only that which is essential for the functioning of proteins involved in oxygen transport, oxidative energy production, mitochondrial respiration, and DNA synthesis, while minimizing the potential for iron toxicity from its redox cycling. These homeostatic mechanisms work at 2 levels: firstly at the level of the whole body through interactions of plasma hepcidin with membrane ferroportin and secondly at a cellular level through interaction of iron responsive element (IRE)-binding proteins (IRPs) with IREs present on mRNAs of key iron metabolism–related proteins.

Body Iron Homeostasis

A healthy human contains 40 to 50 mg/kg of iron, mainly as hemoglobin (30 mg/kg). About 4 mg/kg is present in muscle myoglobin, with 2 mg/kg in cells as iron-containing enzymes. Storage iron, present as ferritin and its compact, partially degraded form hemosiderin, ranges from 0 to 2000 mg[1]; this is mainly present in liver, spleen, and bone marrow (BM) macrophages, formerly referred to as the reticuloendothelial system (RES), and in hepatocytes.[2] Liver iron concentration (LIC) rarely exceeds 1.8 mg/g dry weight (dw) in healthy individuals in the absence of liver disease, hemochromatosis genes, inappropriate dietary supplementation, or blood transfusion.

A healthy individual absorbs only about 10% of dietary iron or about 1 to 2 mg/d, usually balanced by iron loss from skin, gut, menstruation, or pregnancy. Anemia, hypoxia, ineffective erythropoiesis (IE), and the presence of variant HFE genes increase iron absorption, the common factor being low, or inappropriately low, plasma hepcidin levels.[3] The latter permits higher enterocyte ferroportin expression, allowing Fe(II) flux and hence increasing dietary iron absorption. Iron absorption is also increased through hypoxia-inducible factor 1–mediated signaling, by duodenal upregulation of DcytB and DMT1 expression.[4] Thus, in principle, any anemia will tend to increase the efficiency of iron absorption. Most body iron turnover, however, is not directed through iron absorption, but through plasma transferrin, which, although binding only 1 to 2 mg of iron at any moment, in a healthy adult delivers about 20 to 30 mg/d *via* transferrin receptors on the erythron for hemoglobin synthesis.

Hepcidin regulation is important both to iron absorption from diet and to iron egress from erythrophagocytic macrophages. Hepcidin controls iron egress from both macrophages and enterocytes by binding to and degrading ferroportin, through which Fe(II) exits these cells.[5,6] Hepatic hepcidin synthesis is controlled by at least 3 distinct regulatory mechanisms responsive to levels of iron, erythropoiesis, or inflammation.

- Extracellular iron sensing involves the binding of diferric transferrin to transferrin receptor 1 (TfR1), initiating the translocation of HFE from TfR1 to TfR2 and its subsequent signaling via ERK1/ERK2 and p38 MAP kinase to induce hepcidin expression. Storage iron sensing is affected by BMP6 signaling via BMP receptor (and SMADs pathway) whose sensitivity is markedly increased by its interaction with hemojuvelin, HFE, and TfR2 in holotransferrin-dependent manner, thus enhancing hepcidin transcription.[7,8]
- Erythropoiesis sensing involves BM-derived factors that suppress hepcidin synthesis; conditions with high levels of IE will have high levels of these factors, the nature of which has been debated. These include GDF15[9]; twisted gastrulation factor-1[10]; and most recently erythoferrone,[11] which has been identified as a key factor in mice, although its relevance in humans has yet to be demonstrated. Another separate erythropoiesis sensing mechanism likely involves desaturation

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