Iron Balance and the Role of Hepcidin in Chronic Kidney Disease

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Summary: The hepatic iron-regulatory hormone hepcidin and its receptor, the cellular iron exporter ferroportin, constitute a feedback-regulated mechanism that maintains adequate plasma concentrations of iron-transferrin for erythropoiesis and other functions, ensures sufficient iron stores, and avoids iron toxicity and iron-dependent microbial pathogenesis. In chronic kidney disease, inflammation and impaired renal clearance increase plasma hepcidin, inhibiting duodenal iron absorption and sequestering iron in macrophages. These effects of hepcidin can cause systemic iron deficiency, decreased availability of iron for erythropoiesis, and resistance to endogenous and exogenous erythropoietin. Together with impaired renal production of erythropoietin, hepcidin-mediated iron restriction contributes to anemia of chronic kidney disease.

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This article reviews the basics of pathophysiology of iron, focusing on features that contribute to clinical problems in chronic kidney disease. For complementary perspectives the reader is referred to other comprehensive reviews.[1-3]

IRON HOMEOSTASIS

Biological Role of Iron

Iron is an essential trace element that is highly abundant in nature, predominantly in its poorly soluble ferric form. Because iron readily participates in oxidation and reduction chemistry, it has evolved to have an important role in oxygen transport (in hemoglobin), oxygen storage (in myoglobin), energy metabolism (cytochromes), and intermediary metabolism (as a component of many enzymes). Either iron deficiency or iron excess (overload) can have adverse consequences on organ function and tissue integrity. Iron deficiency is the most common cause of anemia worldwide, adversely impacting population health and economic productivity predominantly in developing countries. Severe iron excess can lead to deposition of toxic forms of iron in the liver, heart, and other vital organs, with resulting organ damage, and, in the case of the liver, carcinogenesis.

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Iron Distribution and Flux

In the average adult male there is approximately 4 g of iron, of which 2.5 g is in the hemoglobin of erythrocytes and approximately 1 g is in storage in hepatocytes. The remainder is distributed among other cell types. Iron stores in women are much smaller, even as a proportion of body size. Faced with poor water solubility of iron and its low bioavailability, animals including human beings conserve and recycle iron. Thus, in human beings, iron that is absorbed in the intestine and distributed among tissues is retained and reused, and cannot be excreted actively. Relatively small iron losses (1-2 mg/d) are caused almost entirely by desquamation of the skin and intestinal epithelia, representing a loss of less than 0.1% of total body iron content daily. Under normal circumstances, the iron content of the human body thus is regulated entirely at the point of iron absorption, in enterocytes in the proximal duodenum. In steady state, iron balance is maintained by absorption of 1 to 2 mg of iron per day. However, the daily dietary iron requirement is approximately 10-fold higher because only a fraction of dietary iron is absorbed in the intestine. Clinically significant pathologic iron loss is nearly always a consequence of blood loss because each milliliter of packed erythrocytes contains 1 mg of iron, a vastly higher iron concentration than in other cell types or body fluids. In comparison, blood plasma contains a thousand times lower concentration of iron.

Iron Delivery to Cells

Once absorbed, iron is bound in plasma to the iron carrier protein transferrin, which distributes iron to most tissues and cells in the body. Each cell meets its individual iron needs by selective uptake of iron transferrin via the transferrin receptor, extracting the iron in acidified vacuoles and recycling the receptor

and iron-free transferrin back to the extracellular fluid where the iron-free transferrin is released to extracellular fluid for another cycle of iron binding and delivery. At any time, less than 0.1% of the total body iron (or approximately 2-3 mg) is associated with transferrin. The daily demand for iron is approximately 20 to 25 mg, mainly for erythropoiesis, causing the transferrin-associated iron to turn over every 2 to 3 hours. Within cells, iron is stored in ferritin. The number of transferrin receptors and the amount of iron-storing ferritin in each cell are reciprocally controlled by iron-regulated posttranscriptional mechanisms, thus meeting the iron needs of each individual cell.

Iron Deficiency

Iron deficiency[4,5] develops when the absorption of iron from the diet is insufficient to compensate for iron losses. In adult men in the developed world, with diets that usually contain sufficient iron to balance normal losses, iron deficiency is almost always a pathologic consequence of excessive blood loss. In women, iron deficiency also can develop as a result of menstrual blood losses and iron deficits incurred during pregnancy and childbirth. Iron requirements are greatly increased in children during periods of rapid growth and this can make their iron balance tenuous. The best known and most common manifestation of iron deficiency is microcytic hypochromic anemia, but iron deficiency also can cause neurobehavioral changes, impair muscle function, and may cause epithelial pathologies, including skin, nail, hair, tongue, and esophageal abnormalities. Erythroid heme synthesis, globin chain synthesis, as well as erythroid maturation appear to be inhibited by even moderate iron deficiency through feedback regulatory mechanisms.[6] Slowing down erythropoiesis in iron deficiency may spare enough iron to protect other tissues from dysfunction, at the cost of causing anemia.

Iron Toxicity

Transferrin-bound iron appears to be chemically nonreactive and its uptake and utilization is normally under tight control of each cell. In disorders of iron homeostasis in which iron absorption is excessive, or large amounts of iron are delivered parenterally as drugs or in the form of erythrocyte transfusions, the capacity of transferrin to bind iron may be exceeded (100% transferrin saturation), causing iron to bind to metabolic intermediates that function as iron chelators, mainly citrate. Depending on how these species are measured, they are referred to collectively as *nontransferrin bound iron* or *labile plasma iron*.[7] These iron forms are taken up extremely rapidly by hepatocytes, cardiac myocytes, and endocrine cells via specific iron transporters,[8] overwhelming normal cellular homeostatic mechanisms, and causing cellular toxicity through oxidative stress.

Extracellular Iron Homeostasis

The concentration of iron in extracellular fluid and plasma is controlled systemically, so that the concentration of iron in plasma is normally approximately 10 to 30 μmol/L, leading to 20% to 45% transferrin saturation. The amount of iron in storage, predominantly in macrophages and hepatocytes, also is subject to systemic control. The hormone responsible for regulating extracellular iron concentration and the amount of iron in storage is hepcidin,[3] a small peptide produced by hepatocytes. In turn, the production of hepcidin is regulated transcriptionally by plasma iron concentration, iron stores in the liver, erythropoietic activity, and inflammation. The feedback regulation of iron by hepcidin is a classic endocrine mechanism, analogous to the regulation of glucose by insulin.

The Mechanism of Hepcidin's Effect on Iron

Hepcidin acts by binding to the cellular iron exporter ferroportin,[9] which mediates all the major flows of iron into plasma and extracellular fluid: the transfer of dietary iron from duodenal enterocytes to plasma, the release of recycled iron from splenic and hepatic macrophages, and the release of stored iron from hepatocytes. After hepcidin binds to ferroportin, ferroportin undergoes endocytosis and intracellular proteolysis. The loss of ferroportin from cell surfaces then proportionally decreases the delivery of cellular iron to blood plasma. The ongoing consumption of iron by erythroid precursors and other cells rapidly depletes the relatively small extracellular iron compartment, resulting in hepcidin-induced lowering of plasma iron concentration (hypoferremia). Hepcidin is a hypoferremia-inducing hormone, acting analogously to the hypoglycemic effect of insulin.

Regulation of Hepcidin Secretion by Iron

Systemic hepcidin production appears to be solely transcriptionally regulated. Hepcidin gene transcription is stimulated by the dual effect of liver iron stores and the concentration of plasma holotransferrin (iron-saturated transferrin), conveyed through iron-regulated production of bone morphogenetic proteins (BMP) acting on BMP receptors and the associated Smad pathways.[10] The hepcidin gene promoter contains BMP-responsive elements that bind nuclear Smad complexes to potently increase transcription.

The concentration of the BMP ligand (in mice mainly BMP-6) appears to be regulated by hepatic iron stores.