Disorders of Iron Metabolism and Anemia in Chronic Kidney Disease

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Summary: Dysregulated iron homeostasis plays a central role in the development of anemia of chronic kidney disease (CKD) and is a major contributor toward resistance to treatment with erythropoiesis-stimulating agents. Understanding the underlying pathophysiology requires an in-depth understanding of normal iron physiology and regulation. Recent discoveries in the field of iron biology have greatly improved our understanding of the hormonal regulation of iron trafficking in human beings and how its alterations lead to the development of anemia of CKD. In addition, emerging evidence has suggested that iron homeostasis interacts with bone and mineral metabolism on multiple levels, opening up new avenues of investigation into the genesis of disordered iron metabolism in CKD. Building on recent advances in our understanding of normal iron physiology and abnormalities in iron homeostasis in CKD, this review characterizes how anemia related to disordered iron metabolism develops in the setting of CKD. In addition, this review explores our emerging recognition of the connections between iron homeostasis and mineral metabolism and their implications for the management of altered iron status and anemia of CKD.
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Iron, a trace element with high redox potential (ability to exchange electrons), is essential for the survival of almost all living organisms. It plays a crucial role in the physiology of oxygen transport and its deficiency can lead to anemia and poor oxygen delivery. At the same time, iron's high reactivity can damage proteins and other cell components by formation of oxygen free radicals. For this reason, both cellular and systemic iron homeostasis are tightly controlled. Because iron loss through the gastrointestinal tract is not tightly controlled, maintaining steady iron stores requires precise regulation of iron absorption in the small intestine.

Since the discovery of hepcidin, our understanding of iron homeostasis has grown immensely over the past decade. Hepcidin is the master regulator of iron metabolism,[1] controlling iron transport by binding to the cell-surface iron transporter ferroportin. This results in internalization and lysosomal degradation of ferroportin.[2] Because ferroportin is the only known exporter of iron from mammalian cells, binding of hepcidin to ferroportin in duodenal enterocytes effectively blocks iron absorption from dietary sources by blocking the egress of iron from enterocytes into the circulation. Similarly, hepcidin can reduce iron release from macrophage and hepatocyte stores by blocking ferroportin-dependent export of iron from these cells. Collectively, these actions result in decreased iron availability for erythropoiesis.[2,3]

Circulating hepcidin concentrations are increased commonly in chronic kidney disease (CKD),[4–7] and this is thought to play an important role in mediating the development of anemia of CKD.[8,9] Although inflammation and decreased renal clearance are the major factors underlying increased secretion of hepcidin in CKD, these factors alone do not completely explain high circulating concentrations of hepcidin in CKD. Emerging evidence has suggested that other factors, such as vitamin D deficiency, also may play an important role, as evidenced by experimental data showing direct inhibition of hepcidin expression by vitamin D.[10,11] Iron and vitamin D metabolism also may be linked via effects of iron on fibroblast growth factor 23 (FGF23). FGF23 is a hormone secreted by bone cells that modulates phosphorus homeostasis in part by regulating the activation of vitamin D.[12] Iron deficiency currently is being explored as a potential trigger and a novel mechanism underlying increased FGF23 concentrations in CKD, representing another pathway by which vitamin D may impact iron homeostasis and, ultimately, anemia of CKD.[13,14]

This review focuses on recent discoveries in iron homeostasis and mechanisms underlying disturbed iron regulation in CKD that contribute to the development of anemia of CKD. Furthermore, this review explores

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the emerging connections between dysregulated mineral metabolism and iron homeostasis in CKD.

SYSTEMIC IRON HOMEOSTASIS

Iron Absorption

To balance the obligatory iron losses from the skin and gastrointestinal tract, approximately 1 to 2 mg of iron is absorbed daily from the diet (Fig. 1).[15] Iron absorption takes place in the proximal small intestine where it is tightly regulated. Iron can be absorbed from a typical human diet in its heme or nonheme forms through separate mechanisms.[16] Plants and iron-fortified foods are the primary sources of nonheme iron, whereas heme iron is derived predominantly from meat, seafood, and poultry. Although the human body is well equipped to absorb the heme form of iron more efficiently, the exact mechanism of heme transport into the enterocyte has not been delineated clearly. On the other hand, duodenal absorption of nonheme iron has been studied extensively. Despite the different mechanisms by which enterocytes uptake heme versus nonheme iron across the apical membrane, iron release into the blood across the basolateral membrane uses one mechanism.

Dietary nonheme iron is present predominantly in the oxidized or ferric (Fe^{3+}) form, and before it can cross the apical membrane of the enterocyte, it is reduced to the ferrous form (Fe^{2+}) in a step catalyzed by the brush-border ferric reductase duodenal cytochrome B (Fig. 2).[17] Divalent metal transporter 1 (DMT1), which is present on the apical membrane brush border of the enterocytes, then mediates the uptake of Fe^{2+} iron into the enterocyte.[18] The importance of DMT1 in iron absorption was exemplified in an animal study in which DMT1 knockout mice developed anemia and iron deficiency, which was corrected by parenteral iron infusion.[19] The exact mechanisms by which dietary heme iron is absorbed is less clear but is hypothesized to involve a heme transporter. Once Fe^{2+} is internalized into the enterocyte, it is delivered to the basolateral membrane via mechanisms that have not yet been delineated clearly. Internalized iron also can be added to the cytoplasmic ferritin storage pool, which then can be released from this storage pool in a controlled fashion and delivered to the basolateral membrane.

The basolateral membrane of enterocytes expresses ferroportin.[20,21] Ferroportin-mediated efflux of Fe^{2+} is facilitated by the ferroxidases hephaestin[22] and ceruloplasmin,[23] which convert the exported Fe^{2+} to Fe^{3+}, which then is taken up by the iron carrier protein in the blood: transferrin.

Iron Recycling

Absorbed iron bound to transferrin in the plasma is transported to its sites of utilization (Fig. 1). Each transferrin can bind two atoms of iron as Fe^{3+}.[24]

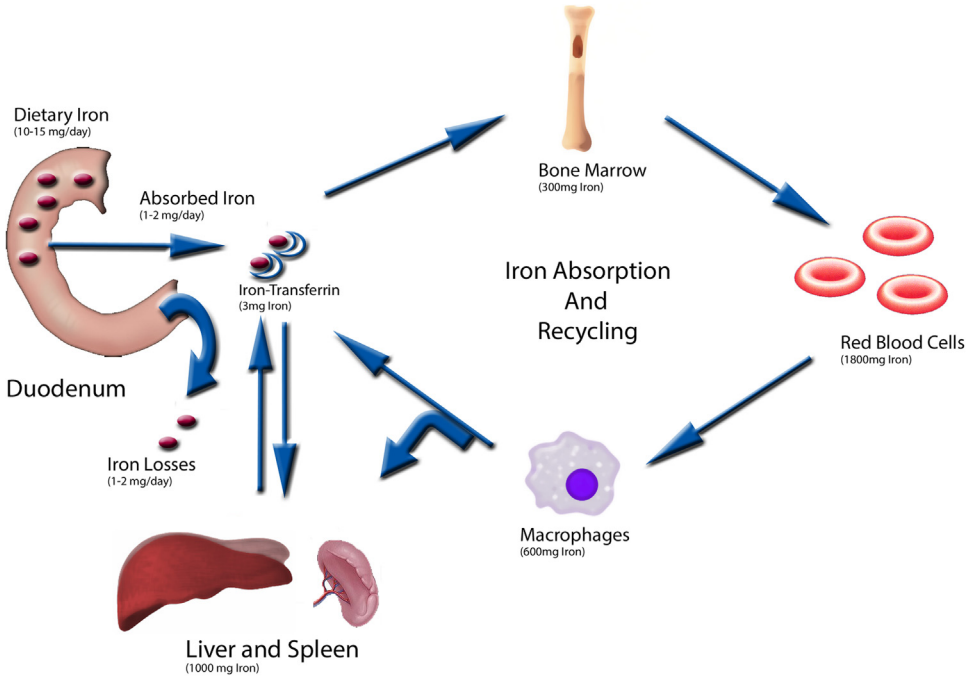

Figure 1. Systemic iron trafficking. Iron is absorbed across the duodenal enterocytes. Once absorbed, it binds to transferrin in the plasma. Iron bound to transferrin then can be transported and taken up by the bone marrow (for erythropoiesis) or the liver or spleen (for storage). Iron is recycled when macrophages take up senescent red blood cells and release iron back to the plasma pool.