Diagnosis of Disorders of Iron Metabolism in Dogs and Cats

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KEYWORDS

• Anemia of chronic disease • Ferritin • Hemochromatosis • Inflammation
• Iron deficiency • Percent saturation • Transferrin

KEY POINTS

- Serum iron concentration is often not an accurate reflection of body iron stores.
- Serum iron concentration decreases with inflammation and iron deficiency.
- Ferritin is currently the best assay for body iron stores.
- Low ferritin indicates iron deficiency; normal ferritin does not rule it out.
- Care must be taken when interpreting levels of ferritin and transferrin because they are acute-phase proteins and inflammation can affect results.
- On a hemogram, MCV_{retic} and CH_{retic} may indicate iron deficiency before MCV and mean cell hemoglobin concentration.

REVIEW OF NORMAL IRON METABOLISM

Function

Iron is an essential element and is used by every cell in the body. Although iron is instrumental in oxygen transport and erythropoiesis, it is also necessary for numerous enzymatic reactions and is important in energy metabolism, DNA synthesis, and cellular immune responses.[1] Contrary to its importance, iron can also cause cell damage with the formation of reactive oxygen species; therefore, its regulation is tightly controlled.[2]

Location

Most total body iron is found within heme, predominantly as hemoglobin of erythroid cells and myoglobin of muscle with lesser amounts within enzymatic hemoproteins. A significant amount of total body iron can also be in storage. Within cells, the most important iron storage protein is ferritin. Much of stored iron is present within

This article originally appeared in Veterinary Clinics of North America: Small Animal Practice, Volume 43, Issue 6, November 2013.
Disclosures: The author has nothing to disclose.
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Clin Lab Med 35 (2015) 579–590
http://dx.doi.org/10.1016/j.cll.2015.05.007 **labmed.theclinics.com**
0272-2712/15/$ – see front matter

hepatocytes. Macrophages in the spleen, liver, and bone marrow can also store large quantities of iron. Hemosiderin, formed by partial degradation of ferritin, is less soluble and may become more abundant than ferritin when iron stores are high.[3]

Plasma Iron

Very little iron (<0.1% of total body iron) is actually in circulation. This iron is mostly bound to the iron transport protein, transferrin, and is turned over multiple times each day. Iron circulating in plasma is predominantly recycled iron from senescent erythrocytes that have been phagocytized by reticuloendothelial macrophages. Only a small amount of plasma iron comes from ingestion, which is the only natural route for taking iron into the body.[1] Small amounts of iron are routinely lost with the shedding of enterocytes, uroepithelial cells, and skin cells and can also occur with blood loss and sweating. Normally, the amount of iron loss about equals the amount absorbed from diet.[2]

Regulation

The regulation of body iron content occurs at the level of absorption by enterocytes because there are no known significant routes of excretion. The amount of iron that is absorbed from diet is controlled by the iron regulatory hormone hepcidin, which works as a negative regulator. It has recently been shown that the acute effect of increased hepcidin concentration is proteosomal-mediated degradation of DMT1, the apical transporter, which normally allows inorganic iron to enter the enterocyte from the intestinal lumen (**Fig. 1**).[4] Therefore, when hepcidin concentrations are elevated, less iron is able to enter the enterocyte, whereas at low hepcidin concentrations, DMT1 is available for transport.

After iron is absorbed by enterocytes from the intestinal lumen, this iron cannot be released to the systemic circulation without a different membrane transport protein on the basolateral membrane of the enterocyte, called ferroportin (see **Fig. 1**). How much ferroportin is available for transport is also dependent on hepcidin concentrations; more ferroportin is available with low hepcidin concentrations and less ferroportin with high hepcidin.

Hephaestin is a ferroxidase expressed on the basolateral membrane of duodenal enterocytes and associated with ferroportin (see **Fig. 1**). Its only known function is to mediate the reoxidation of Fe^{2+} to Fe^{3+} as iron leaves the enterocyte. Exported iron is immediately bound to transferrin for transport through the circulation. Transferrin is a glycoprotein with high affinity for one to two Fe^{3+} ions.

The general mechanism by which hepcidin has been shown to decrease ferroportin numbers has been by binding to ferroportin, which results in internalization and degradation of the membrane transport protein, although new data suggest that hepcidin may influence ferroportin expression on enterocytes by an alternative route, possibly at the level of translation.[4] In addition to enterocytes, ferroportin is also present in the membranes of hepatocytes and macrophages. Ferroportin is the only known membrane protein that exports inorganic iron from mammalian cells and hepcidin seems to be the principal factor in determining ferroportin numbers. Hepcidin, therefore, not only affects serum iron concentration through its effects on enterocytes, but also causes sequestration of iron within macrophages and hepatocytes, preventing efflux of iron into plasma (**Fig. 2**).

The factors that influence the concentration of hepcidin (and, therefore, the extracellular movement of iron) include iron status and the amount of body iron stores, tissue hypoxia, erythropoiesis, and inflammation.[5] Plentiful iron and inflammation result in increased hepcidin transcription, whereas anemia, hypoxia, and iron deficiency suppress its expression. An excellent review of hepcidin has recently been published.[5]