Review

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# Iron metabolism and related genetic diseases: A cleared land, keeping mysteries

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## Summary

Body iron has a very close relationship with the liver. Physiologically, the liver synthesizes transferrin, in charge of blood iron transport; ceruloplasmin, acting through its ferroxidase activity; and hepcidin, the master regulator of systemic iron. It also stores iron inside ferritin and serves as an iron reservoir, both protecting the cell from free iron toxicity and ensuring iron delivery to the body whenever needed. The liver is first in line for receiving iron from the gut and the spleen, and is, therefore, highly exposed to iron overload when plasma iron is in excess, especially through its high affinity for plasma non-transferrin bound iron. The liver is strongly involved when iron excess is related either to hepcidin deficiency, as in HFE, hemojuvelin, hepcidin, and transferrin receptor 2 related haemochromatosis, or to hepcidin resistance, as in type B ferroportin disease. It is less involved in the usual (type A) form of ferroportin disease which targets primarily the macrophagic system. Hereditary aceruloplasminemia raises important pathophysiological issues in light of its peculiar organ iron distribution.


## Introduction

Iron is the best and the worst thing for the human body. Iron is deeply involved in a number of critical metabolic processes, a lack of this metal impairs body functioning, especially in the haematological domain. Conversely, excessive body iron is the source of multiple cellular and visceral damage. These two "mirror" hazards explain why iron homeostasis is a crucial need for the body. For this physiological purpose, a myriad of metabolic actors, particularly proteins, are involved in iron metabolism. Structural and/or functional disturbances of these actors, of acquired or genetic origin, may cause severe diseases relating to either an iron deficiency or an iron overload. The liver plays a key role in iron homeostasis, not only as the source of major protein actors, among which transferrin, ceruloplasmin, and mostly hepcidin, but also as the main iron storage organ and a preferential target of iron overload toxicity [1]. Although the iron domain has benefited from major advances, a number of issues remain to be solved.

### Key points

- The liver produces most proteins of systemic iron metabolism: transferrin (plasma iron transport), ceruloplasmin (plasma iron delivery), haptoglobin (linkage with haemoglobin), hemopexin (linkage with free heme), and hepcidin, the master regulator of iron homeostasis.
- The liver is a major iron storage organ, concerned mostly by parenchymal (hepatocytic) but also by macrophagic (Kupffer cell) iron deposition.
- Non-transferrin bound iron (NTBI) is avidly taken up by hepatocytes and is toxic through its reactive form (labile plasma iron-LPI).
- The liver accumulates iron and undergoes its toxicity mainly in hepcidin deficiency-related haemochromatosis (types1, 2, and 3 haemochromatosis).
- The liver is less impacted by iron overload in the usual form of the ferroportin disease (type 4-A haemochromatosis).
- The mechanisms whereby hepatocytic iron deposition occurs in hereditary aceruloplasminemia are not fully elucidated.
- Hyperferritinemia is the usual diagnostic call sign for iron overload, and its interpretation requires a rigorous approach.

Keywords: Iron; Transferrin; Ferritin; Hepcidin; Ceruloplasmin; Ferroportin; Erythroferrone; Non-transferrin bound iron; Hemojuvelin; Transferrin receptor; Haemochromatosis; Liver.
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**Iron metabolism: "The ten iron laws"**

Iron homeostasis is governed by inescapable laws. A failure to follow these rules, especially due to inborn errors, favors the development of iron metabolism diseases [2–4].

*Iron is not dispensable*

Total body iron load normally approximates three to four grams. Two-thirds of this iron quantity are contained in red blood cells, within the haemoglobin molecules. Iron (Fe) is part of the porphyrin ring of the heme molecule, and has a major ability for linking oxygen [5]. Erythrocytic iron circulates in the plasma and delivers oxygen to all cells, while being itself delivered to the bone marrow in order to contribute to the daily production of approximately 200 billion of new red blood cells [6]. Therefore, iron plays a major role in the respiratory process, and without iron, the human body could not breath. This is as truer as iron is also involved at the cellular and molecular levels, in the respiratory chain which serves to the generation of energy through ATP production. The muscle, through iron incorporation inside myoglobin, has a special place in this energy process. Iron is also involved in multiple enzyme activities catalysing metabolic processes such as xenobiotics biotransformation, lipid metabolism, collagen production, or DNA synthesis.

*Iron is not produced by the body which is therefore exposed to iron deficiency*

The only iron source is alimentary. A normal diet provides 10–20 mg per day, of which only one tenth (1–2 mg) is absorbed [4]. Within the digestive tract, iron exists under two forms: heme iron (meat, fish) and non-heme iron (cocoa, cereals with the highest content in lentils). As to spinach, its iron content is far from initially (erroneously) reported (the "Popeyes' syndrome"...), but remains significant since it is close to that of meat. Iron is absorbed at the duodenal level and this absorption process is approximately five times more efficient for heme iron than for non-heme iron.

Chronic lack of dietary iron unavoidably leads to iron deficiency. Two main situations are concerned. If digestive absorption is normal, deficient alimentary input is either "absolute" (malnutrition) or "relative" (increased physiological iron needs, especially during infancy, adolescence, pregnancy, and lactation). The second mechanism is defective iron absorption. It may be due to alimentary co-factors which are capable of decreasing iron absorption (for example, tannins contained especially in tea and at a lesser degree in coffee, or phytates contained in seeds, legumes, and nuts) or to increase it (vitamin C [7]). These co-factors interfere preferentially with non-heme iron absorption. Beside the role of co-factors, defective iron absorption may be related to damage of the absorption process itself (corresponding to malabsorption, such as occurring in coeliac disease [8]).

*The fate of iron after intestinal absorption is mainly the erythrocyte (Fig. 1)*

Once iron has crossed the digestive barrier, at the duodenal level, it reaches the blood, is linked to its carrier protein transferrin, and

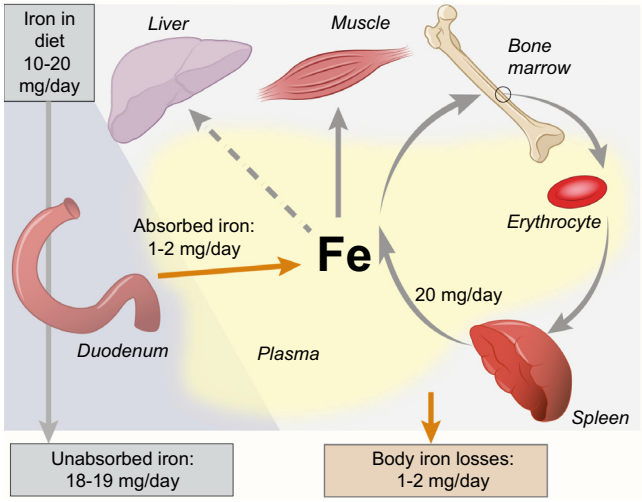


**Fig. 1. Iron homeostasis.** Plasma iron comes from duodenal absorption and from the spleen (iron recycling following erythrophagocytosis).

is predominantly (up to 80%) directed toward the bone marrow. It enters the erythroblasts via transferrin receptor 1 and undergoes the classical transferrin iron cycle. The remnant part (20%) goes into the various extramedullary cells in order to participate in many metabolic processes (respiration, xenobiotics biotransformation, DNA synthesis).

*Iron cannot circulate within the body or be stored in a free form*

Being a metal, iron is neither soluble in the plasma nor in the cytosol. Therefore, it must be linked to other molecules in order to avoid toxicity due to the ability of iron to generate reactive oxygen species (ROS).

In the blood, plasma iron is physiologically taken up by transferrin, with a normal linkage ratio between the theoretical capacity of iron binding to transferrin (2 iron atoms per transferrin molecule) and plasma iron concentration of less than 45% (transferrin saturation [TS]). Whenever TS increases over 45%, new circulating iron species can appear, named non-transferrin bound iron (NTBI) [9]. NTBI has a very special kinetics. In contrast with transferrin iron, it targets preferentially – and with very high affinity – the parenchymal cells, especially the hepatocytes [10,11]. NTBI uptake by the hepatocytes involves mostly solute carrier SLC39A14 (ZIP14) [12,13]. This NTBI is not a "free" iron but is likely linked to low molecular weight ligands (citrate, acetate) or to carboxylic groups of albumin [14]. When TS exceeds 75%, a peculiar NTBI form, called labile plasma iron (LPI) or reactive plasma iron, defined by its capacity for producing ROS, may appear. It corresponds to a potentially toxic form of circulating iron [15–19]. Iron can also be transported by indirect systems, such as haptoglobin, binding haemoglobin, and hemopexin, binding free heme (coming from intravascular hemolysis).

In the cytosol, iron is essentially stored inside the ferritin molecules. Each ferritin molecule may store up to 4500 iron atoms. Ferritin acts as an iron "sponge", storing the metal in case