

Discuss human iron homeostasis in health

Body Iron distribution

Body iron approximately 4-6 g

Erythrocytes: 2500 mg (70%)

Iron stores: 1000 mg (25%) in Bone marrow, liver and spleen (RES)

Other tissues: 250 mg (5%)

Plasma: 4mg (0.1%)

Iron Homeostasis:

“Closed System”

Iron loss equals absorption and therefore precarious balance especially pre-menopausal menstruating women

Haem absorption

Minor role

Haem Carrier Protein (HCP1): Duodenal Brush Border

Intracellular haem is converted to Fe (II) iron and enters a common for intracellular pathway

Iron absorption

About 10% (1 mg) from Average diet which contains 10-20 mg/day

Mainly in meat and fish

Predominantly duodenal for inorganic iron (90%) and haem iron (10%).

Mechanism of iron absorption

Transcellular absorption

- Luminal phase
- Uptake and processing by duodenal mucosal cells (enterocyte)
- Transfer of duodenal mucosal iron into plasma

Luminal phase:

Iron is made available for absorption in duodenum

Increased absorption

- Ferrous >> ferric
- Low pH
- Reducing agents (Vitamin C)
- Ligands (aminoacids, citrate)
- Iron deficiency, hypoxia

Decreased absorption

- Achlorhydria/alkalosis
- Inhibitors: Phytates, tanins, antacids,
- DMT Competitors: Drugs (tetracyclines), heavy metals (Pb)
- Iron overload

Uptake and processing by duodenal enterocyte

- Ferric reductase (Dcytb) in brush border : Fe (III) -->Fe (II)
- Carrier protein (divalent metal transporter 1-DMT1): Fe (II)

Intracellular iron is then

- Transferred to basolateral membrane

or

- Incorporated intracellular ferritin and shed back into gut.

Cellular control

The intracellular iron concentration controls the interaction of cytosolic iron regulatory proteins (IRPs) with iron regulatory elements (IREs ; which act as iron sensors in mammalian cells).

Low Plasma Fe → Low Cellular Fe → IRP binds & inactivates IRE → Increased Fe absorption & reduced ferritin synthesis

High Plasma Fe → Hi Cellular Fe → IRP does not bind IRE → Reduced Fe absorption & increased ferritin synthesis

Transfer of intracellular mucosal iron to the plasma

- Ferroportin 1: basolateral membrane transporter
Inhibited by Heparidin
- Hephaestin – Transmembrane bound ferrioxidase: Fe (II) → Fe (III)
- In plasma, Fe (III) circulates bound to transferrin to sites of usage and storage

Plasma

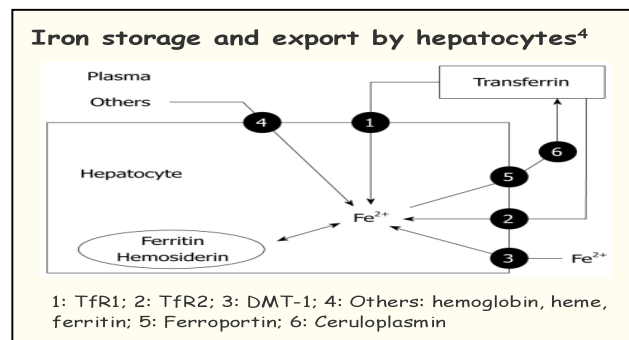
Transferrin has two binding sites for iron atom each (thus 3 forms can be found in plasma: apo-transferrin, monoferric-transferrin and diferric-transferrin). About 30%-40% of these sites are normally occupied

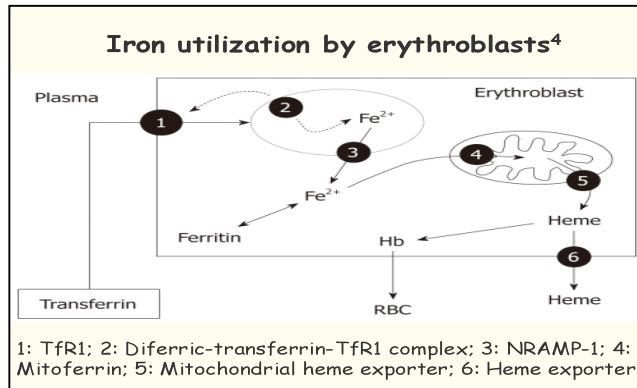
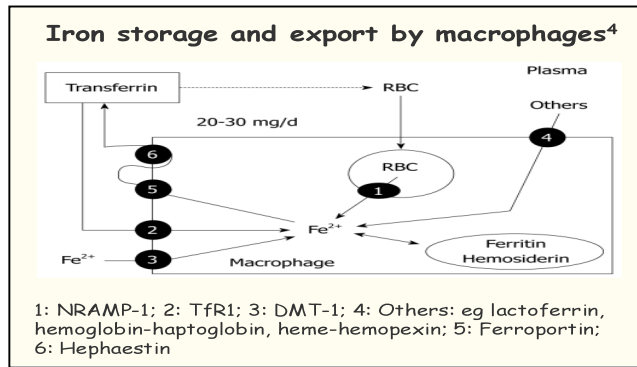
Tissue Import and export

Two transferrin receptors (TfR 1 and 2)

Diferric-transferrin has a much higher affinity for **TfR 1** than does monoferric-transferrin, it binds to the TfR at the plasma membrane, to form clathrin-coated endosomes. After clathrin is removed, the siderosomes become acidified through an ATP-dependent proton influx, which leads to conformational changes in transferrin and TfR1, and promotes iron release of Fe³⁺ from transferrin. Fe³⁺ is then reduced to Fe²⁺ by a ferrireductase and transported to the cytoplasm through the DMT-1, whereas the TfR is recycled to the cell membrane and transferrin shed back to the circulation.

TfR2 appears to be iron sensor which detects transferrin saturation and has a role regulating Heparidin production





Regulatory Role of Hepcidin in iron homeostasis

- Hepatic 25 aa peptide, binds ferroportin decreasing its functional capacity
- Decreased in tissue iron deficiency, hypoxaemia, anaemia and increased erythropoietic activity → Increased iron absorption & release from stores
- Increased in inflammation and tissue iron replete → Decreased iron absorption & release from stores
- Expression regulated by HFE, Haemojuvelin & TfR2
- Types 1-3 Haemochromatosis associated with inappropriately low hepcidin

Iron Losses

About 1 mg/day mainly gut loss

Minor losses through urine, skin and fingernails