Iron metabolism:

Iron is essential for many metabolic processes. It has two properties of particular importance in biology:

1. The ability to exist in more than one oxidation state.
2. The ability to form many complexes.

Iron ability to exist in more than one oxidation state (both ferric and ferrous states) underlies its role in:

1. Enzyme reactions concerned with oxygen and electron transport.
2. The cellular production of energy.

The insolubility of ferric iron means that although the earth's crust contains approximately 4% iron and iron may be plentiful in the diet, much of this is biologically unavailable and iron deficiency is the most common cause of anemia throughout the world.

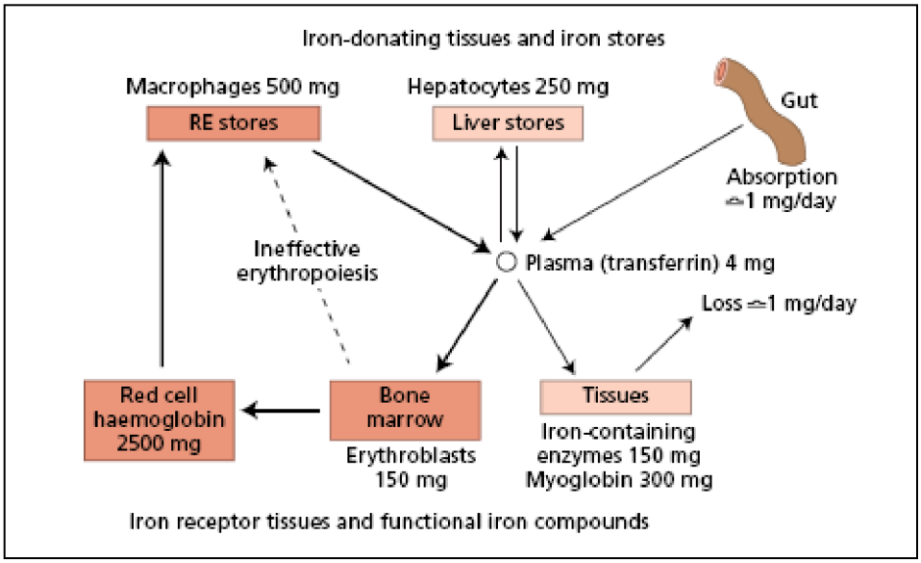
The general need to conserve the metal is reflected in the *absence of any physiological mechanism for excretion of iron*, control of iron balance being at the level of iron absorption only.

Iron absorption depends on:

1. The amount of iron in the diet.
2. The type (bioavailability) of iron in the diet.
3. The body needs for iron.

The concentration of iron in the adult human body is normally about 50 mg/kg in males and 40 mg/kg in females. The largest component is circulating hemoglobin, with 450 ml (1 unit) of whole blood containing about 200 mg of iron. Much of the remainder is contained in the storage proteins, ferritin and

hemosiderin. These are found mainly in the reticuloendothelial (RE) cells of the liver, spleen and bone marrow (which gain iron from breaking down red cells), and in parenchymal cells (which normally gain most of their iron from the plasma iron-transporting protein, transferrin).



This figure shows the major compartments of iron. Iron supply for erythropoiesis and release of iron from senescent red cells dominate internal iron exchange.

Ferritin: Is the primary iron storage protein and provides a reserve of iron. It is water soluble and consists of a spherical apoprotein shell enclosing a core of ferric iron (up to 4000 iron atoms). In normal subjects, the majority of storage iron is present as ferritin.

Hemosiderin: Is, unlike ferritin, a water-insoluble crystalline, protein–iron complex, visible by light microscopy when stained by the Prussian blue (Perls') reaction. It has an amorphous structure, with a higher iron to protein ratio than ferritin.

Transferrin: Is a protein synthesized predominantly by the liver, synthesis being inversely related to iron stores. Two atoms of ferric iron bind to each molecule. Although transferrin contains only about 4 mg of body iron at any time, it is vital to iron transport, with over 30 mg iron passing through this compartment each day.

Transferrin receptor: The uptake of iron from transferrin requires that the protein is attached to specific receptors on the cell surface that act as the homeostatic iron sensor, regulating hepcidin synthesis in response to diferric transferrin concentration.

Serum soluble transferrin receptor: Is not affected by chronic disease and rises proportionally to the degree of iron deficiency. So its measurement can be used as a discriminating assay for Iron deficiency anemia.

Hepcidin: There is direct regulation of iron absorption by hepcidin. This is predominantly expressed in the liver and is downregulated when iron stores are reduced and upregulated when iron stores are increased or by inflammation. Hepcidin is the *predominant negative regulator of iron absorption in the small intestine and iron release from macrophages*. In anemia of inflammation, hepcidin production is increased up to 100-fold, and

this may account for the defining feature of this condition, sequestration of iron in macrophages.

Dietary and luminal factors: Much of dietary iron is non-haem iron derived from cereals, with a lesser component of haem iron from meat and fish which is absorbed much better.

Even in iron deficiency, the maximum iron absorption from a mixed diet is no more than 3–4 mg daily. This figure is much less with the predominantly vegetarian.

Iron is released from protein complexes by acid and proteolytic enzymes in the stomach and small intestine, and haem iron is liberated from hemoglobin and myoglobin.

Iron is *maximally absorbed from the duodenum and less well from the jejunum*, probably because the increasingly alkaline environment leads to the formation of insoluble ferric complexes.

Therapeutic ferrous iron salts are well absorbed on an empty stomach.