Lecture Notes

UJ | SCHOOL OF MED

PHYSIOLOGY

Dr Saleem Khresha

019

النادي الطلابي
كلية الطب

IRON METABOLISM

- Because iron is important for the formation not only of hemoglobin but also of other essential elements in the body (e.g., myoglobin, cytochromes, cytochrome oxidase, peroxidase, and catalase); it is important to understand the means by which iron is utilized in the body.
- The total quantity of iron in the body averages 4 to 5 grams.
- Iron can be found either in ferric (fe+3) or ferrous (fe+2) state, but the body can utilize ferrous state only.
- The average daily iron intake is about 20 milligrams daily (usually) , but the amount absorbed by our body is 3-6% of the amounts ingested, this means that we ingest more than we need, and most of the iron in our diet is in the ferric state.
- Dietary iron takes two major forms:
  1. iron that is part of a heme moiety
  2. iron that is not

  So iron is either heme or non-heme.

- Overall iron absorption is low; 10% to 20% of ingested iron is absorbed (this information is mentioned in the slides), and heme iron is absorbed more efficiently than non-heme iron.
- body stores of iron depend almost exclusively on iron absorption because we don't have a regulated pathway for iron excretion.
- Dietary iron comes primarily from meat (liver and fish)as well as vegetables.

Non-Heme Iron

- Non-heme iron can be either in ferric or ferrous state, but ferric iron tends to form salt complexes with anions quite easily and thus is not readily absorbed, also it is not soluble at pH values higher than 3, but on the other hand, ferrous iron doesn't form complexes easily and it is soluble at pH values as high as 8.

- Regarding vitamin C (ascorbic acid), it can form complexes with iron that are soluble, and it also reduces iron ferric to the ferrous stat , so it enhances iron absorption.

- Iron movement does not occur passively but requires one or more proteins to facilitate its movement into and out of cells (especially enterocytes, hepatocytes, and macrophages) as well as for intracellular binding.

Very Important Note:

the absorption of non-heme iron is restricted only to the duodenum .

But how does the absorption occur?

1. The enterocytes take up non-heme iron across the apical membrane (lumen of the intestine) through Divalent Metal Transporter **-DMT1-.**

2. This transporter Cotransports Fe+2 and H+ into the cell.

In the case of dietary ferric iron , which our enterocytes can't absorb, it will be reduced via Ferric reductase Dcytb - related to cytochrome b – at the extracellular surface of the apical membrane, then it will be taken into the enterocytes through DMT-1.

3. After the movement of Fe+2 into the cytoplasm of enterocyte, it will bind to mobilferrin (intracellular protein) that will carry Fe+2 to the basolateral membrane, so Fe+2 will be translocated across this membrane through ferroportin transporter.

4. After the exit of fe+2 from the enterocyte, fe+2 needs to be oxidized. This will happen by the action of ferroxidase hephaestin (which is a homologue of the plasma protein ceruloplasmin which carries copper), fe+2 will be oxidized into fe+3, then it will bind to transferrin to be carried in the blood.

5. Once in the circulation, nonheme iron bound to transferrin is ultimately deposited in all the tissues of the body, but it has a particular predilection for the liver and reticulo-endothelial system. Inside these cells, it binds to the protein apoferritin to form ferritin, the major storage form of iron.

6. Smaller amounts of storage iron exist in an insoluble form called hemosiderin.

- Heme Iron is Derived from myoglobin and hemoglobin, heme iron is also absorbed by duodenal epithelial cells.

- Heme iron enters the cells either by binding to a brush border protein or through an endocytotic mechanism. Inside the cell, heme oxygenase enzymatically splits the heme iron, thus releasing free Fe+3 (the doctor said fe+3 but actually heme oxygenase will produce fe+2)

NOTE: iron absorption occurs through the whole small intestine, the most efficient absorption occurs in the duodenum (because they have high capacity to absorb iron), but most of the body supply of iron comes from jejunum because it is the longest part of the small intestine, so the absorption is at its peak in duodenum, then jejunum , then the ileum .Small amounts of iron can be absorbed in the large intestine.

Iron requirements: The amount of iron required each day to compensate for loses from the body and growth varies with age and sex; it is highest is pregnancy and in adolescent and menstruating females. Therefore, these groups are particularly likely to develop iron deficiency if there is additional loss or prolonged reduction intake.

Table 3.3 Estimated daily iron requirements. Units are mg/day.

	Urine, sweat, faeces	Menses	Pregnancy	Growth	Total
Adult male	0.5–1				0.5–1
Postmenopausal female	0.5–1				0.5–1
Menstruating female*	0.5–1	0.5–1			1–2
Pregnant female*	0.5–1		1–2		1.5–3
Children (average)	0.5			0.6	1
Female (age 12–15)*	0.5–1	0.5–1		0.6	1–2.5

*These groups are more likely to develop iron deficiency.

Table 3.1 The distribution of body iron.

Amount of iron in average adult	Male (g)	Female (g)	Percentage of total
Haemoglobin	2.4	1.7	65
Ferritin and haemosiderin	1.0 (0.3–1.5)	0.3 (0–1.0)	30
Myoglobin	0.15	0.12	3.5
Haem enzymes (e.g. cytochromes, catalase, peroxidases, flavoproteins)	0.02	0.015	0.5
Transferrin-bound iron	0.004	0.003	0.1

Iron absorption

Factors favoring	Factors reducing
Ferrous form	Ferric form
Inorganic iron	Organic iron
Acids-HCL, vitamin C	Alkalis- antacids, pancreatic secretions
Solubilizing agents- e.g. Sugars, amino acids	Precipitating agents- phytates, phosphates
Iron deficiency	Iron excess
Increased erythropoiesis	Decreased erythropoiesis
Pregnancy	Infection
Primary haemachromatosis	Tea
	Desferrioxamine

Causes of Iron deficiency

1. Blood loss (through GI tract such as peptic ulcer, piles, and aspirin ingestion, excessive menstruation)
2. Increased demands such as prematurity, growth, and pregnancy.
3. Malabsorption such as gastrectomy, celiac disease.
4. Poor diet.

- Hemoglobin is made from proteins so in protein deficiency the hemoglobin synthesis will be affected.

- Trace elements such as copper and cobalt (cobalt is constituent of vitamin b12 and copper is part of proteins, hormones, and enzymes).

- Bone marrow is the place where erythropoiesis occurs, so healthy BM means normal erythropoiesis.

- Hormones play role in erythropoiesis such as erythropoietin, androgens, thyroid hormones, growth hormones, and corticosteroid hormones.

Hemoglobin synthesis

- Hemoglobin consists of protein (96%) and heme (4%).
- Regarding Hb concentration; 16 g/ 100 ml of blood in males but 14 g/ 100 ml of blood in females.

- Each Hb molecule contains 4 subunits ; 2 alpha , 2 beta ; the alpha subunits contains 141 AA , but beta contains 146 AA.

- 65% of Hb synthesis occurs in erythroblast (nucleated cells) and 35% occurs in reticulocytes.

- The heme part carries oxygen and CO (causes toxicity in the blood and may cause death), but the proteinous part carries CO2, H+, and 2.3 BPG.

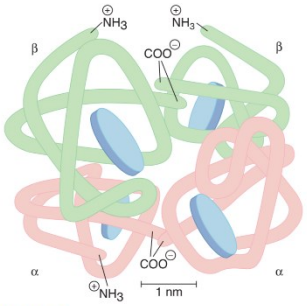


FIGURE 32–6 **Diagrammatic representation of a molecule of hemoglobin A, showing the four subunits.** There are two α and two β polypeptide chains, each containing a heme moiety. These moieties are represented by the disks. (Reproduced with permission from Harper HA et al: *Physiologische Chemie.* Springer, 1975.)

NOTE: 4 subunits, each subunit carries heme, so the total amount of oxygen carried is 4.

Steps of Hb synthesis

1. Heme part : glycine + succinyl CoA gives ALA by ALA synthase which uses vitamin B6 (this step is stimulated by erythropoietin and inhibited by Heme (negative feedback)). The end product is protoporphyrin which is added to iron and will give us heme.

2. Globin part: synthesis occurs in the ribosomes because it is a protein, 2 alpha 2 beta + heme gives us HbA1

NOTE: if anything affects the production of those 2 parts, the synthesis of Hb will be affected.

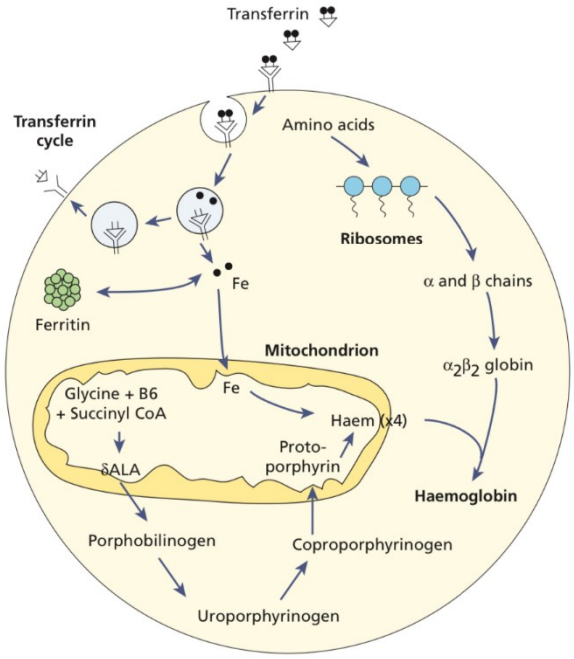
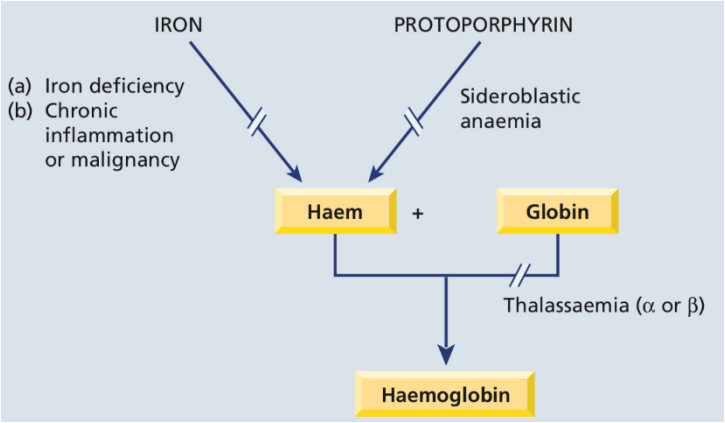


Figure 2.6 Haemoglobin synthesis in the developing red cell. The mitochondria are the main sites of protoporphyrin synthesis, iron (Fe) is supplied from circulating transferrin; globin chains are synthesized on ribosomes. δ-ALA, δ-aminolaevulinic acid; CoA, coenzyme A.

Causes of hypochromic microcytic anemia

Here the cell size will be lower and the cell content of Hb will be lower.

1. Sideroblastic anemia (protoporphyrin is affected).
2. Iron deficiency and chronic inflammation or malignancy (affects heme).
3. thalassemia alpha or beta (affects globin).



Some Notes from the lecture

1. Iron deficiency is estimated to affect about 30% of the world population.
2. Iron deficiency Anemia is still the most important deficiency related to malnutrition.
3. Iron deficiency anemia (IDA) and thalassemia (TT) are the most common forms of microcytic anemia.
4. Some discrimination indices calculated from red blood cell indices are defined and used for rapid discrimination between TT and IDA.
5. Iron-deficiency anemia (IDA) is a common clinical problem throughout the world and an enormous public health risk in developing and even in industrialized countries.
6. Traditionally, several methods other than serum ferritin were used to assess IDA.

Done By :

Abdullah Bilal

Corrected By :

Dana Tarawneh