Sheet No. 3

Physiology

Hematolymphatic System

WRITER: 019

CORRECTOR: Farah mherat

DOCTOR: Dr. Salim Khraisha

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, Enzymes like: cytochrome oxidase, peroxidase, and catalase), it is important to understand the means by which iron is utilized in the body.

o The total quantity of iron in the body averages from 4 to 5 grams.

o Iron is found either in the oxidized ferric (Fe^{3+}) form or in the reduced ferrous (Fe^{2+}) form that is absorbed more easily by our bodies

o most of iron are in ferric form

o The normal iron intake is typically 20 mg/day, yet 10% to 20% of the ingested iron is absorbed (That is what is written in the slides and it's more accurate. However, the doctor mentioned in the video that only 4% is absorbed)

o Dietary iron exists in two forms:

1. Heme iron, in which iron is bound as part of a heme group found in hemoglobin and is present in meat.
2. Non-heme iron (ferric iron) or inorganic iron which is present in plants.

o Heme iron is absorbed more efficiently than non-heme iron.

o Body stores of iron depend almost exclusively on iron absorption because no regulated pathway for iron excretion exists.

o Ferric iron tends to form salt complexes with anions quite easily and thus isn't readily absorbed, it is not soluble at pH values higher than 3.

o Ferrous iron does not complex easily and is soluble at pH values as high as 8.

o Ascorbic acid (vitamin C) forms soluble complexes with iron and reduces it from the ferric to the ferrous state, thereby enhancing iron absorption.

o 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.

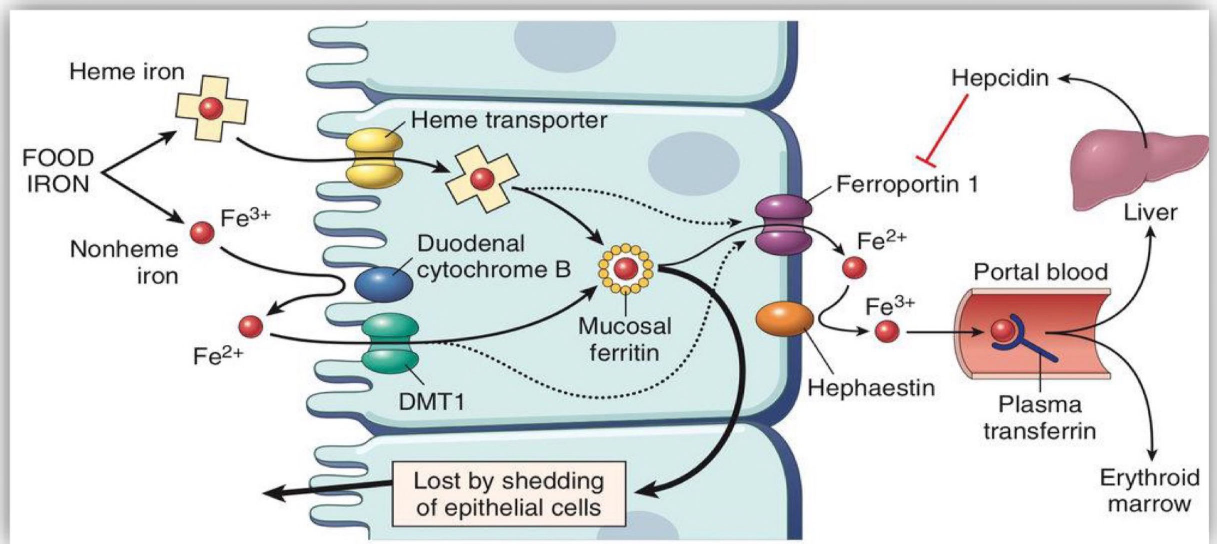
o The absorption of nonheme iron is restricted to the duodenum.
o Absorption of heme iron occurs through the whole small intestine, mainly in the duodenum as it has the highest capacity to absorb iron, then the jejunum comes second, and ileum is the lowest. However, most body supply of iron comes from the jejunum because it's much longer than the duodenum , and very little amount absorbed in colon

o **Steps of iron absorption:**

1. the enterocyte takes up nonheme iron across the apical membrane through the divalent metal transporter DMT1, which cotransports iron and hydrogen into the cell.
2. In the case of the dietary ferric iron, the ferric reductase Dcytb (Duodenal cytochrome B) presumably reduces Fe3+ to Fe2+ at the extracellular surface of the apical membrane before uptake through DMT1.
3. Ferrous moves into the cytoplasm of the enterocytes, where it binds to **mobilferrin**, an intracellular protein that carries the Fe2+ to the basolateral membrane.
4. The enterocyte then translocates the Fe2+ across the basolateral membrane, possibly through ferroportin transporter.
5. Following the exit of Fe2+ the enterocyte, the **ferroxidase hephaestin** (homologue of the plasma protein ceruloplasmin which carries copper) apparently oxidizes the Fe2+ to Fe3+ which then binds to plasma transferrin for carriage in the blood.
6. Once in the circulation, nonheme iron bound to **transferrin** is ultimately deposited in the tissues of the body, but it has a particular predilection(preference) for the liver and reticuloendothelial system. Inside these cells, it binds to the protein apoferritin to form **ferritin**, the major storage form of iron.

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

o Heme iron derived from myoglobin and hemoglobin 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 Fe3+. The enterocyte reduces the Fe3+ to Fe2+,then it will bind to mobilferrin , then it will continue in the same manner as nonheme iron.



o Estimated daily iron requirements mg/day:

	Urine Sweat Feces	Menses	Pregnancy	Growth	Total
Adult male Post-menopausal 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

The iron requirement is different depending on the loss of iron.
The intake of iron must be equal to the amount lost daily.
* These groups more likely to develop iron deficiency.

The distribution of body iron: %of total

Hemoglobin	65
Ferritin and hemosiderin	30
Myoglobin	3.5
Heme enzymes	0.5
Transferrin bound iron	0.1

- **Iron absorption:**

Factors favoring	Factors reducing
Ferrous form	Ferric form
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 Tea

Causes of iron deficiency:

- Blood loss:
  Uterine.
  Gastrointestinal. e.g esophageal varices, peptic ulcer, aspirin ingestion, piles.
- Increased demands:
  Prematurity.
  Growth.
  Pregnancy.
- Malabsorption:
  Gastrectomy.
  Celiac disease.
- Poor diet.

Hemoglobin synthesis:

Hemoglobin is synthesized in multiple steps, the heme part (4%) is synthesized in the mitochondria and the cytosol of immature RBCS, while the globin protein parts (96%) are synthesized by ribosomes in the cytosol.

o Hemoglobin concentration:

- 16 gm/100 mL blood in males.
- 14 gm/100 mL blood in females.

o Each hemoglobin molecule contains 4 subunits:
- 2α subunits and each one contains 141 amino acids.
- 2β subunits and each one contains 146 amino acids.

o 65% of hemoglobin synthesis occurs in erythroblasts (nucleated cells).
o 35% of hemoglobin synthesis occurs in reticulocytes.
o The heme part carries O2 and CO (lethal), while the protein part carries CO2,H+, and 2,3-BPG.
o Each hemoglobin molecule can carry four oxygen molecules.

hemoglobin synthesis:

1. Heme synthesis starts with condensation of Glycine and Succinyl CoA in a reaction catalyzed by ALA synthase, this reaction requires vitamin B6.
   - This step is stimulated by erythropoietin and inhibited by heme (product inhibition).
2. Multiple steps will produce protoporphyrin which combines with iron to form the heme part of hemoglobin.
3. The globin part is synthesized by ribosomes.
4. 2α and 2β subunits unite with 4 heme molecules to form HbA.

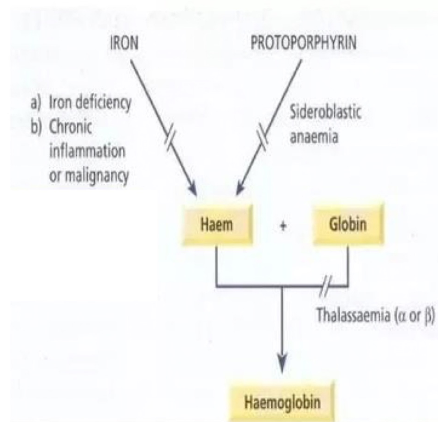
Hypochromic microcytic anemias:

Hypochromic means that red blood cells have less hemoglobin than normal.
Microcytic means that RBCs are small in size because they contain little hemoglobin
So, in Hypochromic microcytic anemias the body has low levels of RBCs that are both smaller and paler than normal.

Causes:

1. Lack of iron (iron deficiency).
2. Lack of iron release from macrophages to serum (chronic inflammation or malignancy).

3. Failure of protoporphyrin synthesis (sideroblastic anemia).
4. Failure of globin synthesis (Thalassemia α or β)



o Iron deficiency is estimated to affect about 30% of the world population.
o Iron deficiency anemia (IDA) is still the most important deficiency related to malnutrition.
o IDA and Thalassemia TT are the most common forms of microcytic anemia.
oSome discrimination indices calculated from RBC indices are defined and used for rapid discrimination between TT and IDA.
o IDA is a common clinical problem throughout the world and an enormous public health risk in developing and even industrialized countries.
o Traditionally, several methods other than serum ferritin were used to assess IDA.

Hemoglobin is basically a protein, so in protein deficiency hemoglobin synthesis is affected.

Trace element (is a chemical element whose concentration is very low a "trace amount"):

1.Cobalt (Co) is one of the vital trace minerals that is known as a constituent of vitamin B12.

2.Copper is an essential trace mineral that is part of proteins, hormones (especially erythropoietin), and enzymes.

— Healthy bone marrow means normal erythropoiesis.

Hormones that affect erythropoiesis:

1. erythropoietin.
2. Androgens.
3. Thyroid hormones.
4. Growth hormone.
5. Corticosteroids.