HEMATOLOGY
&LYMPH SYSTEM

Biochemistry sheet

Number	7
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Iron Metabolism and Absorption

Iron is an important metal that performs essential functions in the body, including being an oxygen carrier and an electron carrier. Iron is present in heme-proteins (hemoglobin, myoglobin, cytochromes, catalase, peroxidase, NO synthase, ..etc) and non-heme-proteins with sulfur centers (ferritin, transferrin, hemosiderin, ferredoxins).

Our bodies contain 3.5 to 5 grams of iron. Two-thirds of such amount is present in the hemoglobin. Ferritin is a storage form, which may form hemosiderin aggregates when Iron levels increase as explained later. 4mg of the body Iron is present in the iron transport protein in the blood, transferrin.

Body content 3.5 to 5 gr

Compartment	Iron Content mg	% total body iron
Hb	2500	68
Storage iron (tissue) (Ferritin, Hemosiderin)	1000	27
Myoglobin	150	4
Other tissue iron [e.g. enzymes]	20	0.6
Transport iron (transferrin)	4	0.1

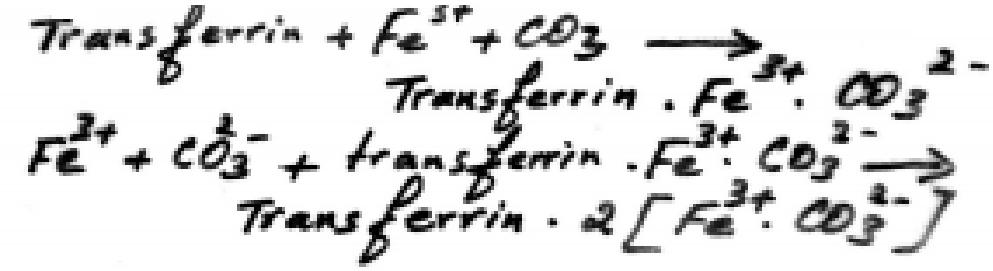
Transferrin

Transferrin, a transport protein, is a glycoprotein that is synthesized in the liver. It is one of the β-globulins of the plasma proteins. It comprises a single polypeptide chain.

The Binding

Transferrin has 2 binding sites, with no cooperativity in binding (independent binding). So, it binds at most 2 iron ions (in the ferric form Fe^{+3}). Transferrin can bind other atoms, but its affinity towards Iron is exceedingly high.

Iron binding is coordinated with the binding of carbonate, as shown:



The association constant of iron-transferrin binding is 10^{-19} to 10^{-31} M^{-1} from different species.

Around 33% of the transferrin is saturated with iron ions. Unsaturated transferrin has an antimicrobial significance, because of the high affinity of transferrin to Iron which allows it to trap Iron, preventing its take up by the microbes. (Numbers are not for memorization.)

Transferrin has receptors on all cells. Transferrin receptor is a trans-membrane protein, which consists of a dimer that is joined with a disulfide bridge. The receptor has an extra-cellular binding segment for the Iron-bound transferrin. Then, internalization of the receptor-ligand complex takes place in a process which depends on a Ca^{++}/Calmodulin protein kinase.

Lactoferrin

This protein resembles transferrin in that it binds iron in the milk. It has an intestinal receptor, and it also has an antimicrobial feature.

Ferritin

Ferritin is a storage protein. Iron must be stored; because free Iron is toxic as it acts as a catalyst in the production of reactive oxygen species (via Fenton

reaction), which can cause tissue damage. Ferritin has 24 subunits, which make a core with a diameter of 130 A^0. It has the capacity to store 4300 iron ions, but it usually contains less number of iron ions. Its heavy chain has ferroxidase activity.

Because of cells shedding and turnover, ferritin can be found in the plasma. Actually, its plasma quantities are of diagnostic importance in assessing the Iron status, as noted later.

0:00 – 10:00

When Iron levels increase, iron gets deposited in ferritin protein. If Iron levels were more than the needed quantities, deposition in ferritin continues, and ferritin, which is a soluble protein, starts forming non-soluble hemosiderin aggregates.

Ferrodoxins

These proteins are non-heme iron-sulfur proteins, in which iron binds to cysteine sulfur or inorganic sulfur atoms. These proteins mediate electron transfer in a range of metabolic reactions.

Iron Absorption

Iron is present in animals and plants. Iron absorption occurs mostly in the duodenum (and also the upper jejunum).

Heme Iron

Heme Iron is more easily absorbed than non-heme Iron. Approximately, 5% of all ingested non-heme Iron is absorbed, while around 20% of ingested heme Iron is absorbed.

Non-heme Iron

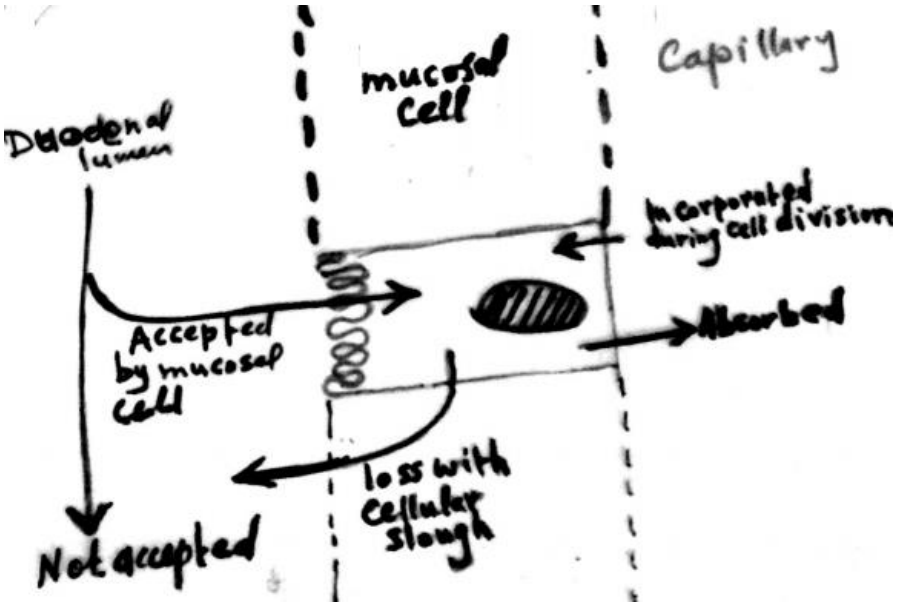
Ferrous ion is the absorbed form. In plants, Iron is usually bound to organic compounds in ferric form, which makes it hard for the Iron to be absorbed. For example, spinach is very rich with Iron which is tightly bound to phytate (inositol hexaphosphate), but a small proportion of such Iron is absorbed by the mucosal cells.

Factors that affect non-heme Iron absorption include:

1- Low PH: Gastric acid is needed to mobilize the Iron from the proteins and turn it into the reduced form (ferrous).
2- Ascorbic acid and glutathione turn the Iron into the ferrous form and also help in the dissociation.
3- Oxalate, inorganic phosphate, antacids and tannin (in tea) bind the Iron and decrease its absorption.
   So, when taking Iron supplements, they must not be taken with tea, but instead with orange juice or lemon juice.

Regulations and Kinetics

The regulation of the absorption occurs at the level of mucosal cells and of the capillaries' interface.



Minimal Daily Iron Requirements

	Amounts must be Absorbed, mg	Minimal amount must be ingested mg
Infants	1	10
children	0.5	5
Young, nonpregnant women	2	15-20
Pregnant women	3	30
Men and Postmenopausal women	1	10

This table shows the minimal iron requirements in different age-gender groups. For example, or an adult male, we need 10 mg daily, and only 1 mg is absorbed. Therefore, put in mind that most of the ingested iron is not absorbed. And here are some numbers from the slides.

500-550 mg iron / 1 L blood
20-40ml blood loss/each menstrual period
" → loss of 11 to 32 mg iron
→ 0.35 to 0.9 mg loss/day

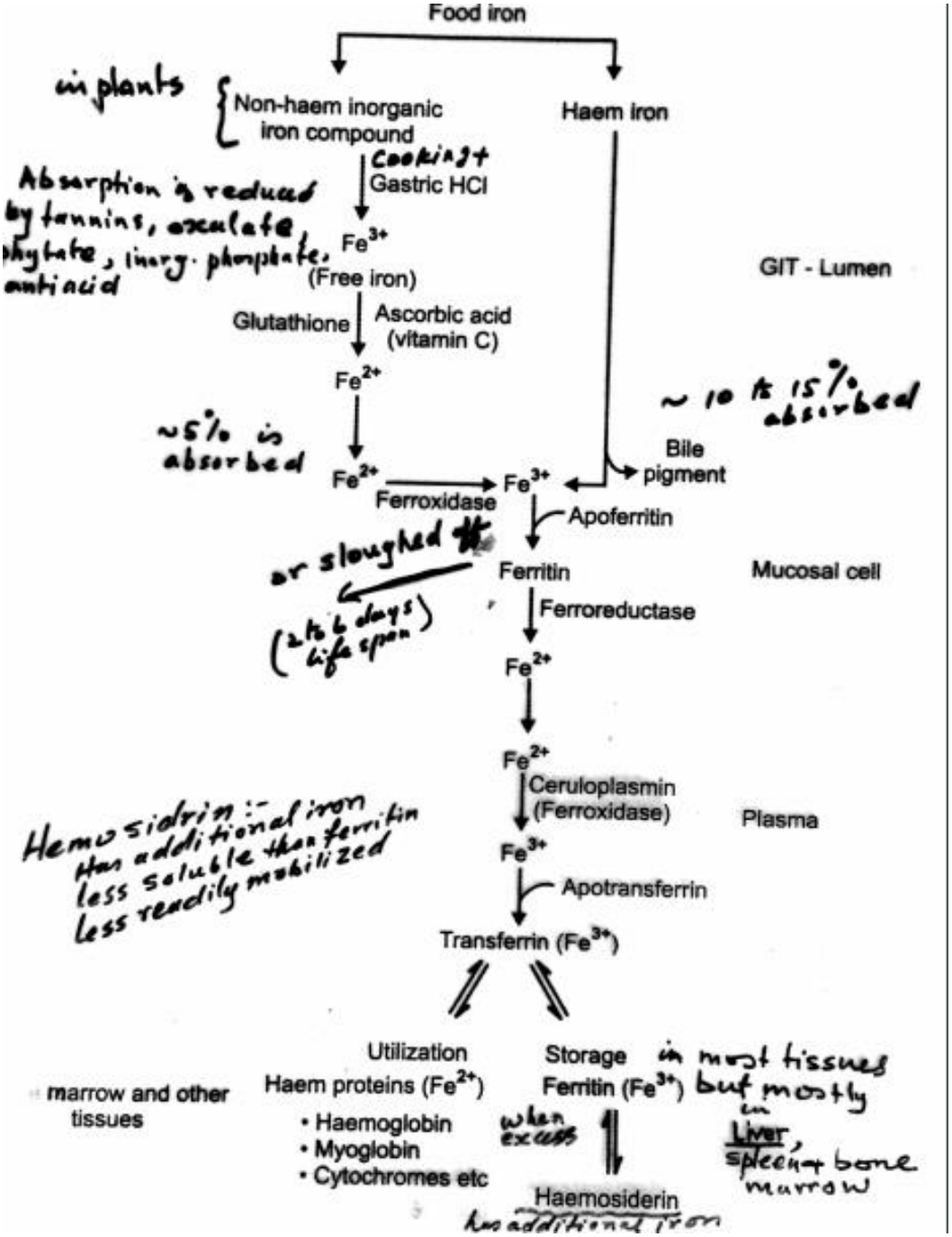
250-300 mg → fetus during pregnancy
gg-900 mg → placenta and cord, blood loss during birth

100-180 mg lost during lactation

Iron loss is maximal during the third trimester of pregnancy
~ 5 mg/day

Absorption, Storage and Utilization of Food Iron

First, the ingested non-heme Iron, which has been dissociated from proteins (by gastric acidity), gets reduced to the ferrous form (by ascorbic acid and glutathione), which is the absorbable form. After the mucosal cells take up the ferrous iron, it gets oxidized to the ferric form by activity of ferroxidase. Then, these ions bind ferritin if not needed.



The turnover of each mucosal cell occurs after 6-7 days. So, the cells get sloughed with the iron they contain. So, the iron gets back again to the intestinal lumen, and gets secreted with feces. So, if excess iron is absorbed, it gets stored in the mucosal cells till it is needed again or gets eliminated with the cells shedding.

If iron is needed, ferritin releases the iron, which gets reduced to the ferrous form (by ferrireductase) to leave the cells. This ferrous iron needs to get oxidized to ferric form to bind transferrin in the circulation. This oxidation is catalyzed either by serum ferroxidase enzyme or ceruloplasmin (a copper protein).

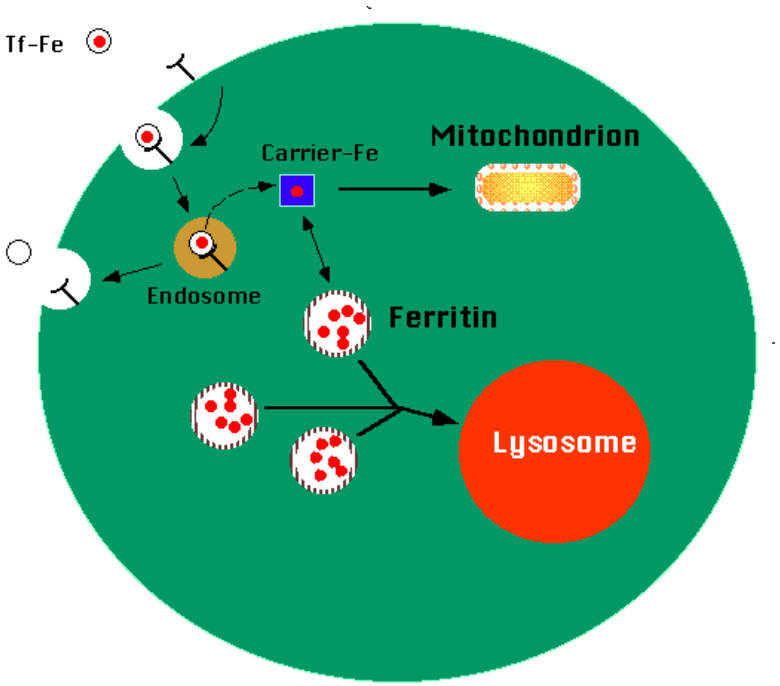
The transferrin-bound ferric ions can by utilized by all cells. They also can be stored in ferritin in generally all cells, especially in the bone marrow, the liver and the spleen. To be stored, it undergoes the oxidation-reduction cycles again.

If iron overload occurs, iron-containing ferritin proteins form the insoluble hemosiderin. Hemosiderin accumulation reflects the iron overload, but it still can be an asymptomatic case. Excessive accumulation can be dangerous.

10:00 – 20:00

<u>Utilization of the Carried Iron</u>

Ferric-bound transferrin has a receptor on the cells. When it binds these receptors, internalization occurs to the receptor-ligand complex, forming an endosome (vacuole) that contains the complex. The endosome has an acidic environment. This leads to the dissociation of the ferric-transferrin complex, and also leads to ferric reduction to form ferrous ions. Thus, this is called the compartment of



uncoupling of receptor and ligand (CURL).

This iron is transported to the cytoplasm by the divalent metal transporter 1(DMT-1). Then, to be stored in ferritin within the cell, it gets oxidized to ferric form. The receptor and the transferrin get recycled and reutilized again.

Regulations

- Iron response element: Iron response element binding protein (IRE-BP) binds the IRE on the 3' end of the mRNA that forms the transferrin receptor, and on the 5' end of the mRNA that forms apoferritin. When Iron is *deficient*, IRE-BP is not bound to iron, and so it is active and binds the mRNAs, protecting transferrin receptor mRNA from nucleases, and prevents apoferritin mRNA translation. When excess iron is present, it binds and inactivates the IRE-BP, so it does not bind the mRNAs, and so apoferritin is produced, and transferrin receptor mRNA is degraded.

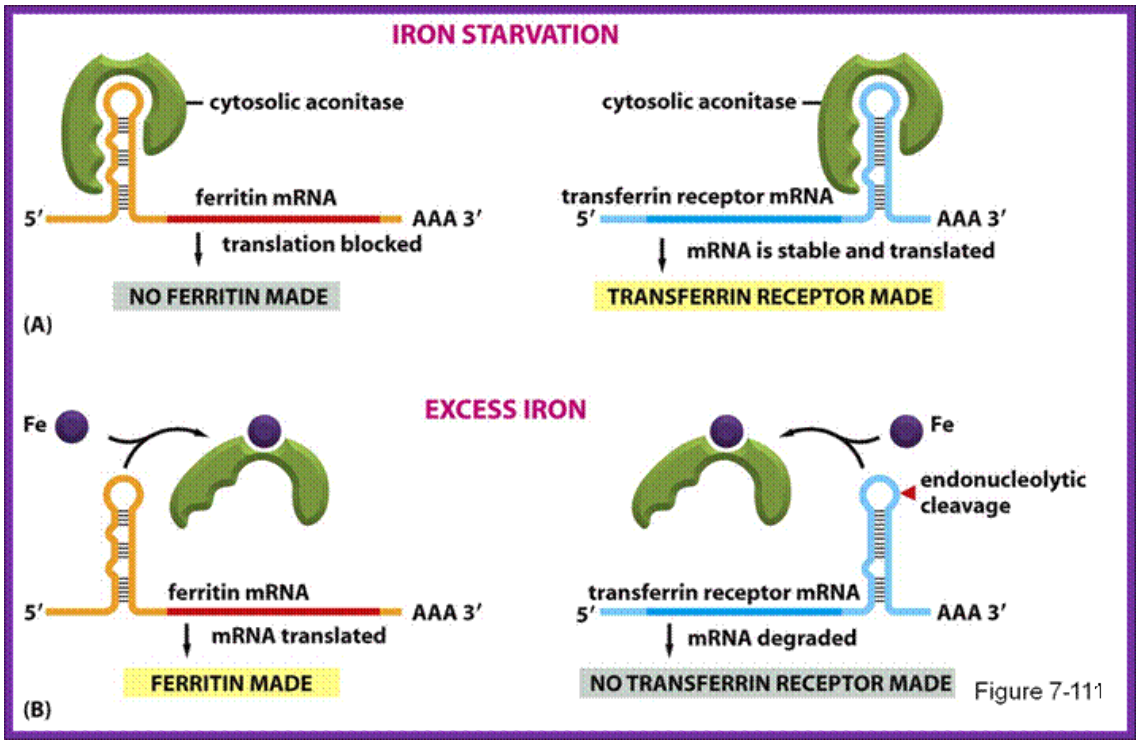


Figure 7-111

Major points:

1- Ferrous form is the one that crosses the cell membranes.
2- Ferric form is the one that binds transferrin and ferritin.
3- Iron reduction is not well understood.
4- Iron is a one-way element; the body has no effective execration (or degradation) pathway for it.

Iron Loss

Iron loss is more common among young females (because of menstruation and pregnancies). In males, iron loss can result from GI bleeding. Iron loss has 3 stages:

1- Initial stage: Iron storage is depleted; ferritin, whose level is the most sensitive for iron loss, is decreased. Transferrin saturation proportion is nearly normal.
2- The second stage: Hemoglobin levels decrease, RBCs undergo morphological changes, and unsaturated transferrin levels increase (= saturated transferrin decreases). Ferritin levels are further decreased. Also, plasma iron is decreased, protoporphyrin in RBC's increases and transferrin carrying capacity increases. [Total iron binding capacity increases as transferrin is not fully saturated.]
   20:00 – 30:00
3- The third stage: enzymes and metabolic markers get defected.

Hemochromatosis (Iron Overload Syndrome)

Hemochromatosis indicates accumulation of iron in the body from any cause and results in hemosiderosis and damage of important organs such as the heart, liver, pancreas, and joints. The most important causes are either primary (hereditary haemochromatosis (HHC), a genetic disorder), or secondary. HHC is the most genetically inherited disease in white populations, with a rate of heterozygosity of 1/4, and homozygosity rate of 1/400.

Secondary causes include:

- Eating high amounts of iron-rich foods (no genetic causes).
- Hemolysis and trans-fusional iron overload, which can result from repeated blood transfusions.

Iron damage results because of iron-catalyzed production of reactive oxygen species. Males are more prone to iron overload than females (especially young females). It is significant to note that alcohol ingestion increases iron absorption, which may worsen the secondary iron overload.

Treatment

- Blood withdrawal is the most effective treatment.
- Iron chelators, which are not as effective as blood withdrawal, but are the only treatment for patients with hemolytic anemia who need regular blood transfusion.

35:00 – 30:00

*Remember that the doctor provided a chapter as a reference for this topic.