(a) A hemoglobin molecule is composed of four protein globin chains, each centered around a heme group.

(b) Each heme group consists of a porphyrin ring with an iron atom in the center.

In most adult hemoglobin, there are two alpha chains and two beta chains as shown.

$R =$ additional C, H, O groups

Iron
IRON METABOLISM & CLINICAL IMPORTANCE
IRON METABOLISM
LEARNING OBJECTIVES

At the end of the lecture, student should be able to;

• Know the biochemical properties of iron
• Enlist the functions of iron in body
• State the sources of iron in diet
• Describe the steps of iron absorption from gut to cells
• Describe its forms of storage in the body
• Know the clinical importance of iron for its regulation in body
Iron is classified as a trace element in the body.

Iron is essential to life because of its unusual flexibility to serve as both an electron donor and acceptor.

Vital element in metabolic process
Deficiency – anemia
Overload - haemochromatosis
BIOCHEMICAL PROPERTIES OF IRON

Essential component of Hemoglobin (Fe$^{+2}$) (ventilation)

Binds reversibly with Oxygen in lung and release Oxygen to tissues.

Binds CO$_2$ to release in lungs.

Methhemoglobin (Fe$^{+3}$)

Cytochromes are essential for electron transport in respiratory chain, (reversible cycling Fe$^{+3}$ to Fe$^{+2}$) for ATP synthesis

Peroxidase & Catalase (iron containing enz) converting harmful H$_2$O$_2$ to H$_2$O.
BIOCHEMICAL PROPERTIES OF IRON

Iron’s high activity is a two-edged sword, and free iron ions in the body also participate in destructive chemistry, primarily in catalyzing the formation of toxic free radicals.

Hence, very little free iron is normally found in the body.
Iron Distribution in the body
(03 – 04 grams)

- Hemoglobin in RBC (Blood/BM) 2500/3000 mg
- Myoglobin & Enzymes 300 mg
- In stores (Ferritin) 1000 mg
- Transferrin 4 mg
- Absorption 1 mg/D
- Losses 1 mg/D

RDA= 1mg/day
Dietary requirement – 10-15 mg/day

Iron exist as Fe$$^{+++}$$ complexed with protein, AA, organic acid or heme)

Food > 5mg/100 gms
  Organ meat, wheat germ, Dried beans

Food 1-5 mg/100 gms
  Muscle meat, fish, fruits, most green vegetables, most cereals

Food <1 mg/100 gms
  Milk and dairy products
FOOD SOURCES (dietary intake 15-20 mg/day)

- Dietary iron is in Fe+++ form
- Iron is absorbed in Fe++ form
- Ferric reductase activity at brush border
Factors affecting absorption

Physical State (bioavailability)

Heme > Fe$^{2+}$ > Fe$^{3+}$

Facilitators

Ascorbate, citrate, amino acids, succinate, gastric acid
(Gastric acidity prevents precipitation of insoluble Fe$^{3+}$)

Inhibitors

Carbonates, Phytates, tannins, soil, clay, laundry starch, antacids, Phosphates, Oxalates
(dietary Ca$^{++}$ decrease effect)

Competitors

Lead, cobalt, cadmium, zinc, copper, magnesium, manganese.
Absorption, Transport, and Excretion

Absorption of iron from the intestine is the primary means of regulating the amount of iron within the body.

10% of the 10 mg/day of dietary iron is absorbed.

Iron for absorption must be in Fe(II) (ferrous) state and bound to protein.

But, Fe(III) is the predominant form of iron in foods, it must first be reduced to Fe(II) by agents such as vit C before it can be absorbed.
In the intestinal mucosal cell, Fe(II) bound by apoferritin, then oxidized by ceruloplasmin to Fe(III) bound to ferritin.

Iron is absorbed into the blood by apotransferrin, which becomes transferrin as it binds two Fe(III) ions.

In plasma, transferrin carries and releases Fe to the BM, where it is incorporated into hemoglobin of RBCs.
IRON UPTAKE
(Mucosal block theory)
IRON ABSORPTION (1 mg/day) 10%

- *Occur in enterocytes of proximal Duodenum.*
- All oxidized iron in Fe$^{3+}$ state is reduced to Fe$^{2+}$ by ferri-reductase enzymes.
- Gastric acidity prevents precipitation of insoluble Fe$^{3+}$
- Entry of iron is promoted by Divalent Metal Transporter (DMT1).
- Heme is absorbed independent of duodenal pH
- Hepcidin influence absorption of iron by down regulation.
ABSORPTION OF IRON
1. iron stores as **FERRITIN**
2. pass across basolateral membrane to be carried to **TRANSFERRIN** through a protein **FERROPORTIN & HEPHAESTIN**
3. Fe 2+ is converted to Fe 3+ by ferrooxidase
4. **HEPCIDIN** act as down regulator
Iron stores as FERRITIN
pass across basolateral membrane to be carried to TRANSFERRIN through a protein FERROPOTIN

Fe ++ is converted to Fe +++ by ferroxidase
IRON TRANSPORT

- Iron is transported to bone marrow via plasma Transferrin (β1 -globulin)
- Transferrin obtains iron mainly from reticulo-endothelial system (RES)
- Only small proportion comes from dietary iron
- Each Transferrin molecule can binds only 2 Fe$^{3+}$ atoms
- Aggregate of binding sites of Transferrin is TIBC (30% saturated).
STORAGE OF IRON

• Stored as Ferritin and Hemosiderin in RES.

• Storage of intracellular iron occurs in liver, skeletal muscle and reticuloendothelial cells.

• *Ferritin* is the major protein used for intracellular storage of iron.
**FERRITIN AND APO-FERRITIN**

- In the cell cytoplasm, iron combines mainly with a protein, *apo-ferritin*, to form *ferritin*.
- **Apo-ferritin** is a large polymer of 24 polypeptide subunits. (binds upto 2,000 iron atoms in the form of ferric-phosphate). *Apoferitin* (mol. Wt. 460,000) with varying quantities of iron combined in clusters to form large molecule. *Ferritin* may contain only a small amount of iron or a large amount. It can easily be detachable.

*This iron stored as ferritin is called storage iron.*
STORAGE OF IRON (HEMOSIDERIN).

• Hemosiderin is composed of ferritin, denatured ferritin, and other materials and its molecular structure is poorly defined.

• The iron present in hemosiderin is not readily available to the cell and thus, cannot supply iron to the cell when it is needed.
After about 4 months in circulation, red cells are degraded by the spleen, liver, and macrophages, which return Fe to the circulation, where it is bound and carried by transferrin for reuse.
FERRITIN AND APO-FERRITIN II

When red blood cells have lived their life span and are destroyed, the hemoglobin released from the cells is ingested by monocyte-macrophage cells. There iron is liberated and is stored mainly in the ferritin pool to be used as needed for formation of new hemoglobin.
A **man** excretes about 0.6 milligram of iron each day, mainly into the feces.

- Additional quantities of iron are lost when bleeding occurs.

- For a **woman**, additional menstrual loss of blood brings long term iron loss to an average of about **1.3 mg/day**.

**Menstrual cycle loss is 20-40 mg of iron**
IRON EXCRETION

No physiological pathway to excrete Iron

- Faeces 80-90% diet
- Sloughing of GI cell 1-2mg
- Menstrual flow 5-40mg
- Pregnancy 350-450mg
- Accidental bleeding 0.5mg/ml or more
IRON METABOLISM, SUMMARY

- Iron absorbed from the intestine is stored as ferritin in intestinal epithelium or transported in plasma as transferrin.

- Erythroid progenitors obtain iron for hemoglobin synthesis from plasma transferrin or from recycling of senescent erythrocytes by macrophages in bone marrow, spleen and liver.

- Iron that is in excess for that required for hemoglobin production is stored in macrophages as ferritin, which can oxidized to hemosiderin. These stores can be released from macrophages in times of need (increased erythropoiesis).
Disorders of iron metabolism are evaluated primarily by

1. packed cell volume,
2. hemoglobin,
3. red cell count and indices,

1. total iron and TIBC,
2. percent saturation,
3. transferrin, and
4. ferritin

IRON PROFILE
Total Iron Content (Serum Iron)
7-25μmol/L (50-160μgm/dl)

- Measurement of serum iron concentration refers specifically to the Fe$^{+3}$ bound to transferrin and not to the iron circulating as free hemoglobin in serum.
Total Iron-Binding Capacity

2-4 g/L (200-400mg/dl)

• *Total iron-binding capacity (TIBC)* refers to the amount of iron that could be bound by saturating transferrin present in the serum or plasma sample.

• Typically, about one-third of the iron binding sites on transferrin are saturated.
Percent Saturation

• The percent saturation, also called the transferrin saturation, is the ratio of serum iron to TIBC. The normal range for this is approximately 20% to 50%,
Transferrin

Transferrin is primarily monitored as an indicator of nutritional status.

As a negative acute-phase protein, its concentration decreases in inflammatory conditions.

**Transferrin or TIBC is increased**
- in iron deficiency

**Transferrin or TIBC is decreased in**
- iron overload and
- hemochromatosis.
- chronic infections and
- malignancies.
Ferritin

**Ferritin is decreased in**
- iron-deficiency anemia and

**Ferritin is increased in**
- iron overload
- hemochromatosis.
- chronic infections,
- malignancy, and
- Viral hepatitis.
# LABORATORY MARKERS OF IRON STATUS IN SEVERAL DISEASE STATES

<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum Iron</th>
<th>Transferrin</th>
<th>Ferritin</th>
<th>% Saturation</th>
<th>TIBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal levels</td>
<td>7-25 μmol/L 50-160 μgm/dl</td>
<td>2-4 g/L 200-400 mg/dl</td>
<td>20-250 μgm/L 250-350 ngm/ml</td>
<td>20-50%</td>
<td>45-75 μmol/L 250-350 μgm/dl</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Iron overdose</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Sideroblastic Anemia</td>
<td>↑</td>
<td>☠☐</td>
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<tr>
<td>Malnutrition</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>variable</td>
<td>↓</td>
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<tr>
<td>Chronic infection</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Malignancy</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Anemia due to Chronic diseases</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
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- **Condi**: Condition
- **Serum Iron**: Normal levels 7-25 μmol/L, 50-160 μgm/dl
- **Transferrin**: 2-4 g/L, 200-400 mg/dl
- **Ferritin**: 20-250 μgm/L, 250-350 μgm/dl
- **% Saturation**: 20-50%
- **TIBC**: 45-75 μmol/L, 250-350 μgm/dl
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<td></td>
<td>250-350 µgm/dl</td>
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<td>Viral Hepatitis</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>☠️↑</td>
<td>↑</td>
</tr>
<tr>
<td>Acute Liver Disease</td>
<td>↑</td>
<td>🕊↑</td>
<td>↑</td>
<td>↑</td>
<td>☠️↑</td>
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Clinical Aspects of Abnormal Iron Metabolism

Both deficiency and excess results in abnormalities

Iron deficiency anemia
Hemochromatosis
• Disorders of iron metabolism
  – Iron deficiency anemia
  – Thalassemia syndrome

• Iron storage disorders
  – Hemosiderosis
  – Hemachromatosis
  – Hereditary hemochromatosis
Thank You

Your thoughtfulness meant so much to me.