

Iron

I. Iron metabolism

A. Iron distributed in six compartments

1. Hemoglobin
 - a. 0.34% iron
 - b. 1ml packed RBC contains approximately 1mg iron
 - c. Total amount is 2-2.5gm
2. Storage iron (ferritin, hemosiderin)
 - a. Ferritin
 - i. Ferric hydroxide within a "bag" or shell of apoferritin
 - ii. Each ferritin contains ~2000 Fe atoms, about 20% by weight
 - iii. Water soluble
 - iv. Electrophoretically distinct types present in different tissues, especially liver, RE system, intestine
 - v. Ferritin synthesis may be induced by iron
 - b. Hemosiderin
 - i. Probably partially denatured ferritin
 - ii. 25-30% iron by weight
 - iii. Water insoluble
 - iv. Present in RE system, but may accumulate widely
 - c. Storage pool contains about 1gm iron in men, about 600mg in women
 - d. Easily mobilized and depleted in iron loss
3. Myoglobin
 - a. Monomer similar to hemoglobin
 - b. Present in skeletal and cardiac muscle
 - c. High O₂ affinity (Oxygen reservoir for periods of local hypoxia?)
 - d. Contains ~130mg iron
4. Labile iron pool
 - a. Concept derived from iron kinetic studies
 - i. Iron leaves plasma and is bound to membrane or cytoplasmic proteins
 - ii. From there, it is incorporated into heme or other structures, or else refluxes into plasma
 - iii. This reflux is seen in curve of ⁵⁹Fe plasma clearance, and from these data, one can calculate the size of the bound "labile" iron pool
 - b. Contains 80-90mg iron
 - c. A widely-distributed, acid-extractable protein of MW ~12,000 is implicated as the binder
5. Tissue iron
 - a. Heme proteins - cytochromes, peroxidases, catalase
 - b. Flavoproteins - xanthine oxidase, dehydrogenases, cytochrome C reductase
 - c. 6-8mg iron
6. Transport iron
 - a. Common pathway by which other compartments are interchanged
 - b. Contains 3mg iron and turns over 10 times per day
 - c. Transferrin - protein responsible for transport
 - i. β globulin
 - ii. Iron binding sites at each end of the molecule
 - iii. The site with the lower affinity is preferentially occupied, as it is recognized more readily by physiologic iron donors
 - iv. Transferrin binds to a specific receptor on the cell membrane, and is internalized into an endosome
 - a). In the endosome, the pH is very low, causing the iron to drop off
 - b). Gallium inhibits this pH change
 - c). Aluminum effect? There is a hypochromic, microcytic anemia associated with dialysis/dementia syndrome.

- v. Transferrin supplied iron required by growing cells
- vi. Apotransferrin synthesized in the liver and RE system
- vii. Congenital atransferrinemia
 - a). Extremely rare, autosomal recessive
 - b). Hypochromic, microcytic anemia with marked hemosiderosis of liver, pancreas, heart, kidneys, thyroid
 - c). Transferrin level 0-10mg/100ml (TIBC 30-80µg/100ml)
 - d). Transient response to plasma or purified transferrin
- viii. Acquired atransferrinemia seen in nephrotic syndrome
- d. Plasma ferritin
 - i. Low concentration, about 100ng/ml (10µg/100ml)
 - ii. Contains 5-7% iron
 - iii. Very rapid turnover, so may be a significant factor in iron transport
 - iv. Plasma ferritin iron increases markedly in those with fully saturated transferrin

B. Absorption

1. Balance

- a. Average daily losses
 - i. 1mg for males
 - ii. 2mg for premenopausal women
 - iii. Add 1mg daily for lactation
- b. Average intestinal absorption is 15-20% in normal subjects
- c. Diet provides 10-20mg per day, some as heme and some as inorganic iron from water and cooking utensils
- d. Not clear whether absorption is the same for organic and inorganic iron

2. Enterocytes lining the proximal duodenum are responsible for iron absorption

3. Mechanism

- a. Transmucosal into blood stream
- b. Intestinal absorption only of Fe⁺⁺. Ferric iron is enzymatically reduced in the intestinal brush border. Transport into the cell is via the enzyme *divalent metal transporter 1* (DMT1), which can also transport manganese, cobalt, copper, zinc, cadmium, and lead. Absorption of heme-bound iron is by a different, poorly-characterized mechanism.
- c. Must be converted into Fe⁺⁺⁺ for binding to transferrin
- d. Heme degraded in mucosal cells to bilirubin, CO, and iron by heme oxygenase
- e. Regulation of absorption
 - i. Most iron bound to intestinal ferritin and trapped
 - ii. Mucosal cells sloughed, taking iron with them
 - iii. This mechanism can be overwhelmed by high intraluminal iron concentration
 - iv. The remainder is transported into plasma. The ratio of trapped/transferred iron is a property of the enterocyte, and probably established by the conditions of iron balance at the time the cell developed. Transport is across the basolateral membrane of the enterocyte.
 - a). TfR-HFE complex. HFE is a protein that is missing in people with hereditary hemochromatosis. It binds with the transferrin receptor on the cell surface, thereby inhibiting cellular uptake of iron.
 - b). Basolateral iron transporter. The products of the genes *Ireg1*/ *MTP1* regulate iron transport across cell membranes. They are preferentially located in mature duodenal enterocytes and hepatic Kupffer cells (responsible for iron scavenging).
 - c). Hephaestin is a protein structurally similar to ceruloplasmin, a copper-containing enzyme required for efficient recycling of iron between liver, reticuloendothelial system, and blood. Hephaestin cooperates with another iron-transporter complex on the enterocyte membrane to facilitate efflux of iron from the cell.

f. Other influences

- i. Gastric juice may enhance or retard iron absorption - there is evidence for both
- ii. Absorption increases with liver or pancreatic disease
- iii. Phosphate, phytates bind iron and decrease absorption
- iv. Reducing substances and alcohol increase absorption
- v. Feedback due to anemia, hypoxia, increased erythropoiesis, low iron stores.
 - a). Iron absorption approximately 50% in severe thalassemic syndromes, 24% in HbH disease, and 19% (normal) in hereditary spherocytosis
 - b). A major difference between these groups is in the degree of ineffective erythropoiesis
 - c). Another difference is in the mode of red cell destruction. In thal, a greater proportion is intravascular, and heme iron thus liberated may be transported to the liver, where it is less readily released for reutilization.
 - d). It is speculated that a breakdown product of erythroid precursors exerts a regulatory influence.

C. Iron transport

1. Iron pathway in body essentially a closed system
 - a. Plasma -> developing red cells
 - b. Marrow -> circulating red cells
 - c. RBC's -> RE system
 - d. RE system -> plasma
2. Transferrin supplies iron to normoblasts
 - a. Actively binds to red cell membrane
 - b. Entry into cell has been demonstrated
3. Ferritin is passed between RE cells and normoblasts by "rhopheocytosis". The direction of transfer is not clear
4. When transferrin is fully saturated, absorbed iron goes to the liver
5. When transferrin is absent, hypochromic, microcytic anemia present with massive visceral iron deposition

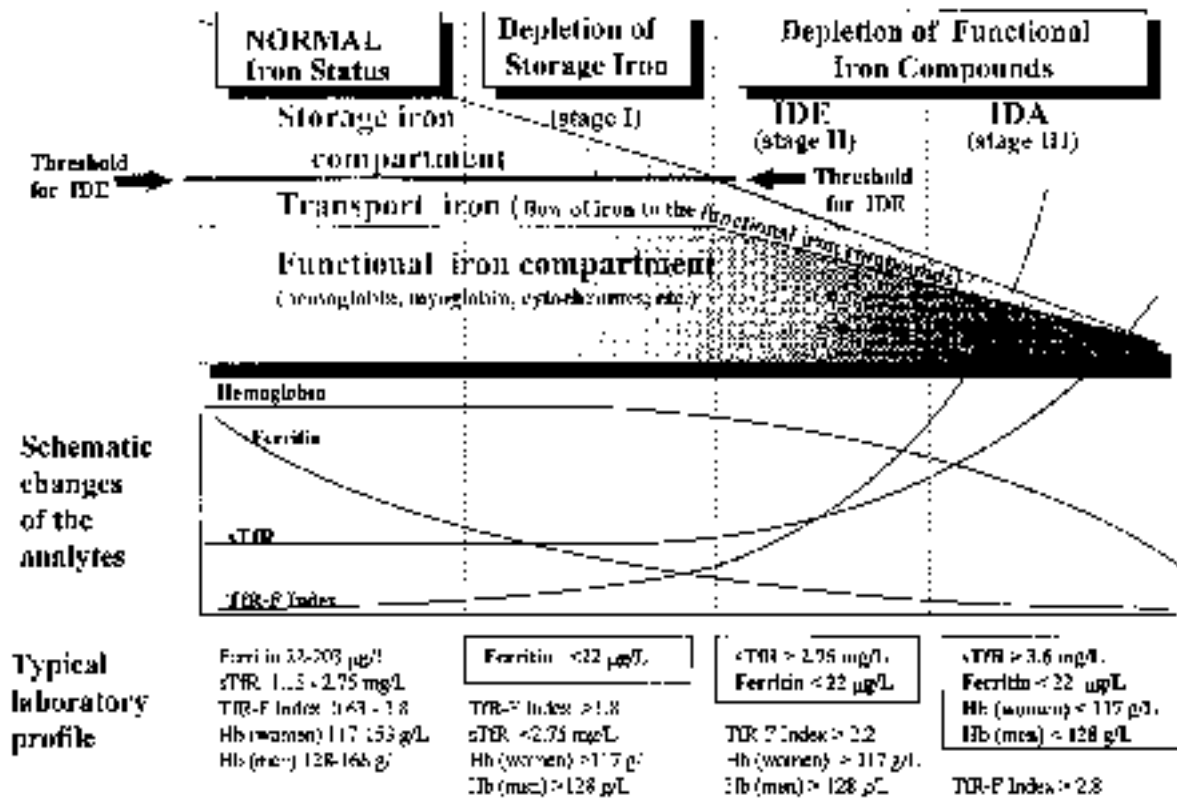
D. RE system in iron metabolism

1. About 20% of RBC iron is available within 2-3 hours
2. 80% of RBC iron rapidly reincorporated into hemoglobin
3. Remainder enters storage pool
4. Turnover altered by rate of RE system release of iron
 - a. Increased when erythropoiesis is increased
 - b. Decreased in infection, inflammation, malignancy
 - c. Mechanism of this regulation not well understood
5. Macrophages both synthesize and ingest transferrin

II. Iron deficiency

A. Degrees of severity

1. Iron depletion
 - a. Absent stores
 - b. Normal serum iron
 - c. Normal hemoglobin
2. Iron deficiency without anemia
 - a. Absent stores



- b. Low serum iron
3. Iron deficiency anemia
- B. Etiology
 1. Dietary deficiency
 - a. Infants
 - i. Require 270 - 280 mg in first year
 - ii. Milk very poor iron source. Cow's milk may actually increase iron loss.
 - b. In American children, overall prevalence is about 3%, but correlates somewhat with socioeconomic status.
 - c. Adults - extremely rare
 2. Malabsorption
 - a. Subtotal gastrectomy
 - i. Bypass of duodenum
 - ii. Rapid transit
 - b. Other
 3. Bleeding
 - a. GI
 - i. Rule out malignancy
 - ii. Association between *H pylori* infection and iron deficiency
 - b. GU - menstrual, tumor
 - c. Hemoptysis
 - d. Epistaxis
 4. Pregnancy

- a. Average loss due to fetal uptake plus hemorrhage at delivery is ~ 900mg
- b. 30mg/month during lactation
- c. Iron depletion occurs in 85-90% of unsupplemented pregnant women
- 5. Intravascular hemolysis
 - a. PNH
 - b. Trauma
 - c. Hemosiderinuria in rheumatoid arthritis
- 6. Parasites
- 7. Chronic renal failure
 - a. Mucosal blood loss due to increased bleeding tendency
 - b. Blood loss in hemodialysis equipment
- C. Incidence
 - 1. May be most common medical condition in the world
 - 2. Up to 20 million cases in USA
 - 3. 35-58% of young, apparently healthy women may be iron depleted
- D. Clinical aspects
 - 1. Often slow development allows adaptation to stress. Symptoms may relate to rate of fall in hemoglobin
 - 2. Poor correlation between hemoglobin level, treatment, symptoms
 - 3. Pica - geophagia, pagophagia, amylophagia
 - 4. Signs
 - a. Pallor
 - b. Smooth tongue
 - c. Stomatitis
 - d. Cheilitis
 - e. Koilonychia
 - f. Splenomegaly
- E. Laboratory aspects
 - 1. Classic picture
 - a. Hypochromic, microcytic anemia
 - b. Low iron, high TIBC, low ferritin, high serum transferrin receptor
 - c. Absent marrow iron
 - 2. Indices usually normal until hemoglobin is quite low (<10gm/dl)
 - 3. Thrombocytosis, especially in bleeding patients
 - 4. May see thrombocytopenia in pediatric age group
 - 5. Bone marrow
 - a. Absent iron stores
 - b. Iron may be present in transfused or parenterally treated patients
 - c. Poor correlation between severity of anemia and M/E ratio
 - d. Iron poorly stored in some patients with myeloproliferative disorders
 - e. Ragged cytoplasm of red cell precursors
 - 6. Serum iron
 - a. Normal is 50-150 or 75-175µg/100ml
 - b. Diurnal variation exists, highest in morning and lowest about 9:00 PM (Regulated by RE release)
 - c. Reduced by inflammation, malignancy, menstruation
 - d. Normal to low with iron deficiency
 - 7. Iron binding capacity
 - a. Normal about 300µg/100ml
 - b. Normal saturation about 33%
 - c. TIBC lowered in chronic disease, so saturation is normal

- d. TIBC raised, and saturation decreased in iron deficiency
 8. Serum ferritin
 - a. Value reflects total body iron stores, although correlation is poor for very high levels
 - b. Value below about 10ng/ml diagnostic of iron deficiency
 - c. Inflammation, liver disease raise ferritin into normal range
 9. Serum transferrin receptor
 - a. Level increases with iron depletion
 - b. Ratio of TfR/log(ferritin), or ferritin index, may be a good discriminator between iron deficiency and anemia of chronic inflammation (Punnonen)
 - c. The simple ratio of serum transferrin receptor to serum ferritin correlates with storage iron (Cook) and can be used to monitor for iron deficiency, at least in those who are not likely to have inflammation.
 10. Free erythrocyte protoporphyrin increased in disorders of heme synthesis
 - a. Iron deficiency
 - b. Pb and other sideroblastic anemias
 11. RBC survival somewhat shortened
 12. Ferrokinetics
 - a. Measured with ^{59}Fe
 - b. Rapid plasma iron clearance
 - c. Increased utilization as hemoglobin
 13. Chelation tests as measure of iron stores
 - a. Inject desferrioxamine
 - b. Measure urinary iron excretion
- F. Differential diagnosis
1. Thalassemia minor
 - a. Smears may be indistinguishable, but thal has more targets, stippling, and polychromasia
 - b. In thal, usually see red count >5 million/ μl
 - c. In thal, MCV usually $55\text{-}70\mu\text{m}^3$
 - d. Hemoglobin electrophoresis (Note that iron deficiency reduces ratio of A_2 and H to A, probably by decreasing α chain production. Competition for α chains is based on electrostatic force, and δ , β^S , etc. don't compete as effectively as β^A .)
 - e. Arithmetic criteria
 - i. $DF = MCV - (5 \times \text{Hb}) - \text{RBC}$ ($> 8.4 \Rightarrow$ iron deficiency, $< 8.4 \Rightarrow$ thal)
 - ii. MCV/RBC ($> 14 \Rightarrow$ iron deficiency, $< 14 \Rightarrow$ thal)
 - iii. MCH/RBC ($> 4.4 \Rightarrow$ iron deficiency, $< 4.4 \Rightarrow$ thal)
 - f. Coefficient of variation (σ/μ) from erythrogram ($> 14\% \Rightarrow$ iron deficiency, $< 14\% \Rightarrow$ thal or normal)
- G. Non-hematological aspects
1. Reduced activity of iron-containing enzymes
 2. Achlorhydria with atrophy of GI mucosa
 - a. Beeturia, the presence of the beet-derived pigment betanin in the urine following ingestion of beets.
 3. Paresthesias, irritability, diminished cognitive performance (esp. in children)
 4. Esophageal webs (Plummer-Vinson)
 5. Impaired activity of skeletal muscle
 6. Abnormal leukocyte function
 - a. T-cell
 - b. Neutrophil killing function
- H. Treatment
1. Oral iron is cheapest and safest

- a. Diet alone is inadequate to replete deficient iron stores
- b. Ferrous salts better absorbed than enteric coated iron
- c. Provide 150-200mg/day of iron, in divided dose
- d. Major toxicity is GI discomfort
- e. Continue for 12 months after anemia corrects

2. Parenteral

- a. Indicated for malabsorption, unreliable patient, or large iron deficit beyond what can be given po
- b. Iron dextran < 70% utilized
 - i. Can give im or iv
 - ii. Test dose of 0.5ml
 - iii. Total dose (mg) = deficit in Hb (gm/100ml) x weight (lb) + 1000mg
 - iv. Side effects
 - a). Anaphylaxis
 - b). Other allergic reactions
 - c). More common and severe in rheumatoid arthritis
- c. Iron sorbitex (sorbitol)
 - i. Administer im only
 - ii. Side effects similar to those of iron dextran
- d. Transfusion
- e. Comparison (from Medical Letter)

<u>Treatment</u>	<u>Cost/gm Fe</u>	<u>Toxicity</u>
FeSO ₄	\$.30	GI
Meat	\$ 150.00	?
Dextran	\$ 30.00	Allergic
Blood	\$ 240.00	Allergic, Infectious

3. Treat the underlying cause

- a. Eradication of *H pylori* may lead to rapid improvement of iron deficiency anemia.

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