Hematology

438 teamwork

Anemia

Color index:

Red: Important

Gray: Extra, notes

Editing file

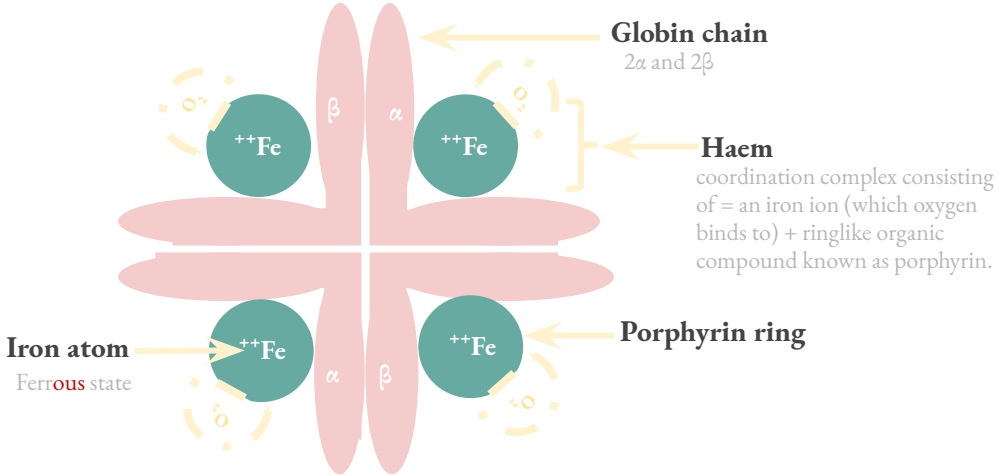
objectives

- To understand the normal control of erythropoiesis
- To understand the pathophysiology of anemia
- To recognize the general features of anemia
- To understand the basis of anemia classification
- To understand iron metabolism
- To understand how iron deficiency
- To understand anemia of chronic disease may arise and how to manage it.

Hemoglobin

- It's the protein molecule in RBC that carries O_2 from the lungs to the body's tissues and returns CO_2 from the tissues back to the lungs.
- Also maintains the shape of RBC.

Hemoglobin structure



Hematopoiesis (formation of blood cells in bone marrow)

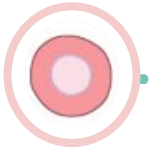
Origin of hematopoietic stem cells is: mesenchymal hemangioblast

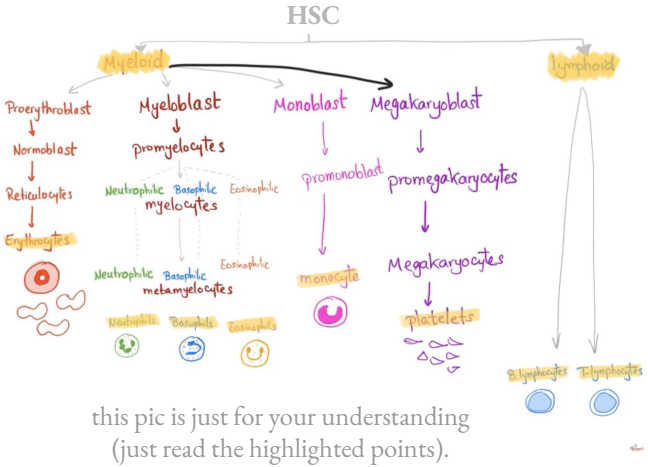
Lymphoid lineages

Other myeloid lineages

Erythroid precursors are the mothers of RBC *not ready yet*

only ready red blood cells gets out of the bone marrow to the circulation.





this pic is just for your understanding (just read the highlighted points).

Hematopoietic stem cell:	Transcriptional Factor
the mother of all blood cells.	these are specific for erythrocytes
Self renewal	Erythropoietin
Cell differentiation	GATA1

transcription factor meaning: a molecule that is capable of changing (increase or decrease) the gene expression in a cell (which is responsible of cell differentiation) by altering the gene transcription.

- Erythropoietin is a hormone controlling the RBC formation.
- 90% synthesized in kidney .
- 10% synthesized in liver.

if there is any abnormality in these two characters of hematopoietic stem cell it will give many diseases like cancer.

Erythropoiesis (RBC formation)

The "Bone Marrow" is the major site with the need of:

- Folic acid
- Vit B_{12}
- Iron "Ferrous"
- Erythropoietin
- Amino acids
- minerals

other regulatory factors

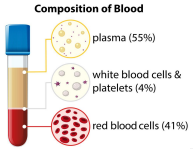
→ Cells under microscope:

Cell						
Name	Erythroblast	Basophilic Normoblast	Intermediate Normoblast	Late Normoblast	Reticulocyte	Erythrocyte
Synthesis of Hb[1]	+	++	+++	++	+	-

Normal Ranges[2]

Indices	Female	Male
Hemoglobin(g/dL)[3]	11.5-15.5	13.5-17.5
Hematocrit (PCV) (%)	36-48	40-52
Red Cell Count ($\times 10^{12}$)	3.9-5.6	4.5-6.5
Mean Cell Volume (MCV) (fL)[4]	80-95	
Mean Cell Hemoglobin (MCH) (pg)[5]	30-35	

HCT Hematocrit



Hb

MCV
- Microcytic
- Normocytic
- Macrocytic

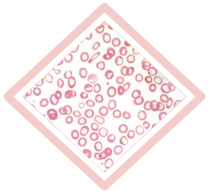
MCH
- Hypochromic
- Normochromic

normally the central ⅓ of RBC is pale

Anemia

- An (without) -aemia (blood)
- Reduction of Hb concentration below the normal range for the age and gender
- Leading to decreased O_2 carrying capacity of blood and thus O_2 availability to tissues (hypoxia)

Classification of Anemia



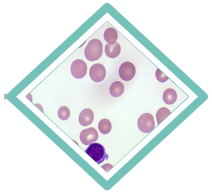
Hypochromic microcytic anemia

Disruption in Hb

-Porphyrin defect. → Sideroblastic anemia

-Iron deficiency. → Iron def. anemia

-Globin chain defect. → Thalassemia



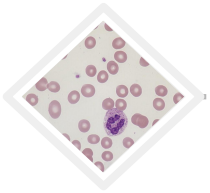
Macrocytic anemia

Disruption of DNA synthesis

↓

Megaloblastic anemia:

- B_{12} def.
- Folate def.
- MDS[6]



Normocytic normochromic anemia

reduction in RBC count

- Blood loss → Acute bleeding
- Hemolysis → Autoimmune, enzymopathy, membranopathy, sickle cell anemia and mechanical[7]
- RBC production → BM failure, anemia of chronic disease[8]

BM failure causes:[9]

- Chemotherapy, aplastic anemia[10] and malignancy[11]

Clinical features[12]

→ Presence or absence of clinical feature depends on:

01

Speed of onset:

- **Rapidly progressive** anemia causes more symptoms than slow onset anemia due to lack of compensatory mechanisms**:**
(cardiovascular system, BM[13] & O_2 dissociation curve)

02

Severity:

- Mild anemia: no symptoms usually
- Symptoms appear if Hb less than 9g/dL

03

Age:

- Elderly tolerate anemia less than young patients due to incompetence of compensatory mechanisms.

General features of anemia

01 Related to anemia

- Weakness
- Lethargy
- Pallor
- Headache
- Dizziness

02 Related to compensatory mechanism of heart

- Palpitation
- Cardiac failure
- Angina

Iron Deficiency Anemia

- Iron is among the abundant minerals on earth (6%).
- Iron deficiency is the most common disorder (24%).

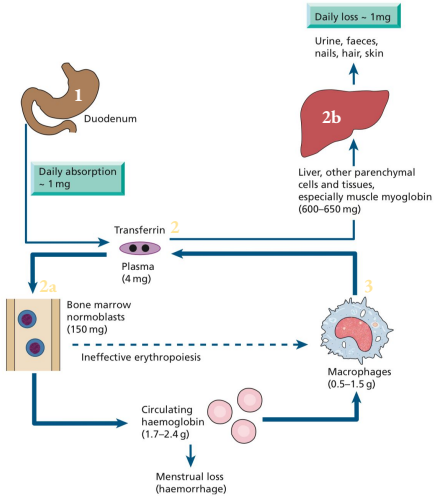
Caused by:

01 Limited absorption ability
- Only 5-10% of taken iron will be absorbed
- Inorganic iron can not be absorbed easily

02 Excess loss due to hemorrhage[14]

→ Explanation

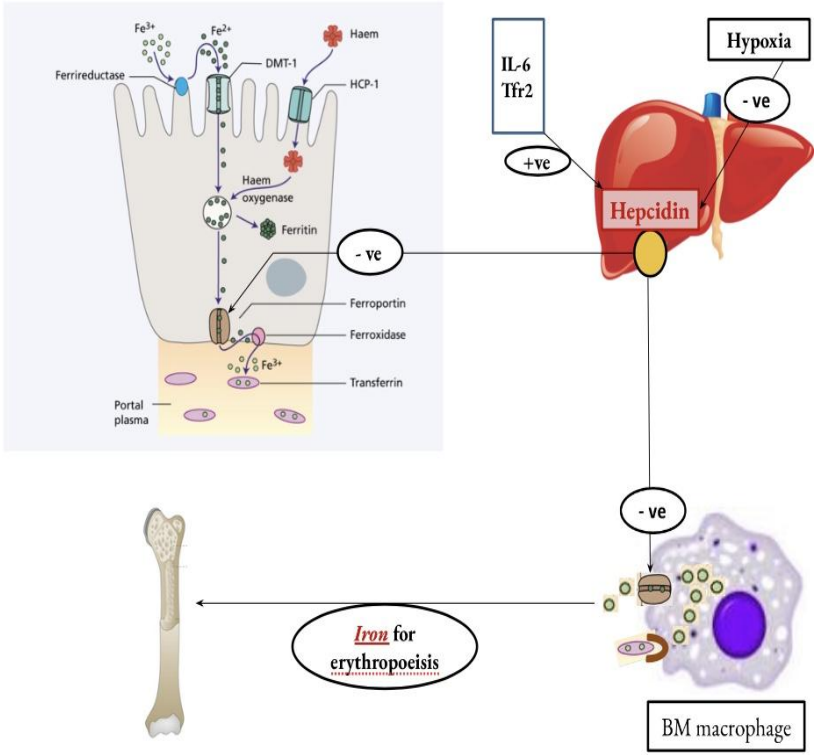
Iron in your body:
*(in a 70kg man the total body iron is about 4g).
*(1 mg is the daily absorbed iron).
*(1mg is daily lost through urine, faeces, nails, hair, skin) other than bleeding and menstrual loss will increase the loss of iron.
*(1.7-2.4 g circulating as a part of Hb on the RBC) THE largest amount of iron is here.
*(0.5-1.5 g within macrophages) macrophages stores a large amount of iron.
*(600-650 mg is stored in: liver, other parenchymal cells and tissues (especially muscle myoglobin).



Storage forms:
Ferritin, Haemosiderin

1- iron is absorbed in Duodenum.
2- Transferrin is a carrier protein, each carries 2 molecules of iron in the form (FERRIC) through circulation to:
A- bone marrow (where Hb is synthesized especially in normoblast)
b- to be stored in liver or muscle myoglobin.
3- phagocytosis by macrophages happens to RBC when:
A- RBC lifespan reaches the end (120 days)
B- when ineffectively formed erythrocytes leaves the bone marrow.
4- iron is stored in liver, muscle and macrophages (BM).
5- iron released from stores when body needed and carried again by transferrin to go to bone marrow.

Iron Deficiency Anemia



Explanation

1- iron absorption is controlled by the hormone hepcidin (synthesized in liver only)
2- the release of this hormone is controlled by
a- IL_6 and Tfr_2 (increase the release of hepcidin)
b- Hypoxia (decrease the release of hepcidin).
3- this hormone is inversely proportional to iron absorption:
High hepcidin = low absorption of Iron.
Low hepcidin = high absorption of Iron.
4- there are many spots controlling the process of iron absorption to prevent iron overload.
5- iron enters the duodenum cells when it gets converted to the ferrous state by the enzyme ferrireductase, then it gets out to circulation in the ferric state by the enzyme ferroxidase so, it can be carried in circulation by transferrin.
6- this hormone blocks ferroportin (the gate of iron to the circulation located in macrophages and duodenum cells).

436 team notes:

(Hepcidin controls Ferroportin by **negative feedback control.**
Inorganic (non-heme) Iron needs to one additional step to be absorbed which is conversion of the Fe^{3+} form (Ferric iron) which is non-absorbable form to the Fe^{2+} form (Ferrous Iron) which is absorbable form by ferrireductase enzyme).

Pathomas

Why hepcidin cause decrease in iron levels?
Hepcidin sequesters iron in storage sites by:
1- limiting iron transfer from macrophages to erythroid precursors
2- suppressing erythropoietin (EPO) production; aim is to prevent bacteria from accessing iron, which is necessary for their survival (as hepcidin is an inflammatory protein hence its effects)

Iron Absorption

01 Body Iron status:

- Increased demands (iron def., pregnancy) → Low iron in stores → High iron absorption
- Iron overload → Full iron stores → Low iron absorption

02 Content and form of dietary iron:

- More iron
- Heam iron
- Ferrous iron

→ More absorption

03 Balance between dietary enhancers & Inhibitory factors:

Enhancers:

- Meat (haem iron)
- Fruit (Vitamin C)
- Sugar (Solubilizing agent)
- Acids

Inhibitors:

- Dairy foods (calcium)
- High fiber foods (phytate)
- Coffee & tea (polyphenols)
- Anti -Acids

Factors affecting absorption

Favoring absorption

1. Heam iron[15]
2. Ferrous Iron (Fe^{2+})
3. Acid
4. Iron def.
5. Pregnancy
6. Hemochromatosis[16]
7. Solubilizing agent (sugar)

Reducing absorption

1. Inorganic iron[17]
2. Ferric iron Fe^{3+}
3. Alkalines
4. Iron overload
5. Tea
6. Increased hepcidin
7. Precipitating agent (phenol)

Causes of IDA

01

Chronic blood loss:

- GIT Bleeding: peptic ulcer, esophageal varices , hookworm & cancer
- Uterine bleeding
- Hematuria

02

Increased demands:

- Immaturity
- Growth
- Pregnancy
- EPO therapy

Erythropoietin

03

Malabsorption:

- Enteropathy
- Gastrectomy

04

Poor diet:

- Rare as the only cause (rule out other causes)

Signs and symptoms of IDA

Beside symptoms and signs of anaemia +/- bleeding, patients present with:

Koilonychia (spoon-shaped nails)

Angular stomatitis and/or glossitis

Dysphagia due to pharyngeal web[19] (Plummer-Vinson syndrome)

Development of IDA

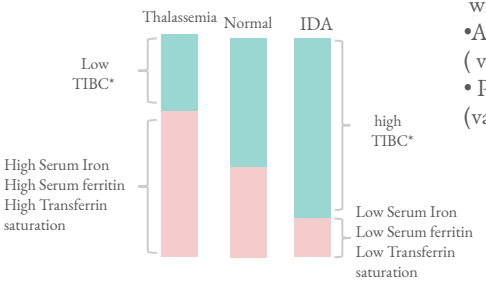
	Normal	Pre-latent	Latent	Iron def. anemia
Stores	Normal	Low	Low	Low
MCV/MCH[18]	Normal	Normal	Low	Low
Hemoglobin	Normal	Normal	Normal	Low

+Signs of anemia

we say it is IDA when we see signs of anemia on top of these results

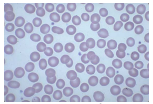
Investigation

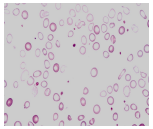
01 Iron Studies



02 Microcytic hypochromic anemia

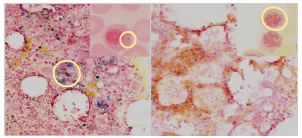
with:
- Anisocytosis (variation in size)
- Poikilocytosis (variation in shape)


Normal


IDA

03 BM Iron stain (Perl's stain)

The gold standard but invasive procedure



Normal Green/blue color = iron

IDA: reduced or absent iron stores (hemosiderin) No green granules in cytoplasm

*TIBC : total iron binding capacity of transferrin

Pathoma:

Total iron-binding capacity: measure of transferrin molecules in the blood

Iron Deficiency Anemia (treatment & prevention)

Treatment of IDA

Treat the underlying cause

Iron replacement therapy:

-Oral :(Ferrous Sulphate OD for 6 months)

-Intravenous:(Ferric sucrose OD for 6 months)

- Hb should rise 2g/dL every 3 weeks

Oral Ferrous Sulphate

Intravenous Ferric sucrose

PREVENTION OF IDA

Dietary modification

Meat is better source than vegetables.

Food fortification (with ferrous sulphate)

GIT disturbances ,staining of teeth & metallic taste.

Iron supplementation

For high risk groups.

Iron supplement

Anemia of chronic disease

Normochromic normocytic (usually) anemia caused by:

➔ decreased release of iron from iron stores due to raised serum Hepcidin.

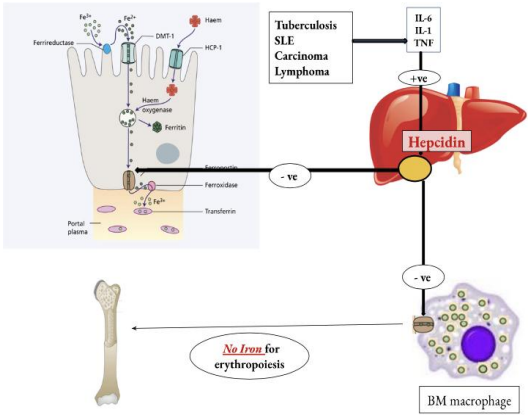
Associated with

01 Chronic infection including HIV, malaria, TB.

02 Tissue necrosis

03 Malignancy: carcinoma, lymphoma.

04 Chronic inflammations



➔ Explanation

Chronic diseases like TB, SLE, carcinoma and lymphoma released a lot of IL-6, IL-1 and TNF these are responsible of the high hepcidin levels which is in turn prevents the release of iron from the stores, so there is NO iron for erythropoiesis.

Features of anemia of chronic disease

01

Normocytic normochromic or mildly microcytic anaemia

02

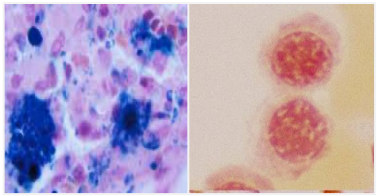
Low serum iron and TIBC

03

Normal or high serum ferritin (acute phase reactant)

04

High haemosiderin in macrophages but low in normoblasts



Management

1. Treat the underlying cause
2. Iron replacement +/- EPO

1- Hb is synthesized in all immature stages but Not in the mature erythrocyte
2- Normal range in CBC depends on (a- sex b-age).
3- Hemoglobin determines the (severity) of anemia.
4- MCV determines the (class) of anemia
5- MCH hypo/normochromic (يحدد نسبة التصبغ)
6- MDS is a malignant hematological disorder called myelodysplastic syndrome
7- mechanical hemolysis likes abnormal heart valves
8- Anemia of chronic disease is a type of anemia that affects people who have conditions that cause inflammation.
9- BM failure is characterized by inability to produce RBC
10 - Aplastic anemia is characterized by bone marrow shutdown
11- Malignancy is very important cause in BM failure especially when metastasis to bone marrow happens
12- If anemia is mild or has developed over a long period of time, there may not be any noticeable symptoms
13-cellularity of bone marrow will increase as a compensatory mechanism if there is enough time (slow onset anemia)
14- Hemorrhages can be due to uterine bleeding, heavy menstrual period...
15- Heam Iron is organic iron like in: red meat (favoring absorption)
16- Hemochromatosis is a congenital anomaly increases the circulating iron,the hepcidin will decrease.
17-Inorganic Iron is found in vegetables: non-haem.
18- this ratio is called RBC indices.

Dr. Notes

19- Dysphagia due to pharyngeal web is membranous folds of tissue that form in the esophagus. this x-ray method is no longer used to diagnose IDA
-During Erythropoiesis, an Erythroblast divides to become 4 Basophilic Normoblasts which then divide to make Intermediate Normoblasts and no more division takes place after this
-In anemia, cardiac failure is due to decreased oxygen capacity which requires more pumping from the heart to meet tissues requirements
-Hypochromic Microcytic anemia happens as a result of lack of hemoglobin which is involved in the formation of the structure of the RBCs (Quantitative deficiency)
-Thalassemia: reduction of production of normal hemoglobin
-Sickle cell anemia: normal production of abnormal hemoglobin
-iron is toxic when it's not bound to a carrier and excessive iron storage in the liver can cause liver toxicity
-in Normochromic Normocytic anemia due to raised serum hepcidin, stool will be full of iron
-normal RBC has to be biconcave, flexible and 8 micrometer in diameter.
-Erythropoietin (EPO) is a hormone that promotes the formation of red blood cells.

Quiz

Key answers:
1-C 2-D 3-C 4-B 5-A 6-C

1- Symptoms of anemia appear when hemoglobin is less than:

A. 7 g\ dL
B. 8 g\dl
C. 9 g\dL
D. None

2- All of the following cause microcytic anemia EXCEPT: ***(from dr.notes)***

A. Iron deficiency anemia
B. Thalassemia
C. Sideroblastic anemia
D. Sickle cell anemia

3- Which one of these factors increase iron absorption?

A. Phytate
B. Phenols
C. Vitamin C
D. Calcium

4- The gold standard stain for diagnosis IDA is: *(from dr.notes)*

A. Silver stain
B. Perl's stain
C. H & E stain
D. Bielschowsky stain

5- Which one of these factors suppress hepcidin activity?

A. Hypoxia
B. IL-6
C. TNF
D. Carcinoma

6- The only form of RBCs that go to the circulation: ***(from dr.notes)***

A. Erythroblast
B. Reticulocyte
C. Erythrocyte
D. Basophilic normoblast

THANKS

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