Iron Metabolism, Iron Deficiency and Overload

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IRON METABOLISM

- Iron has the capacity to accept and donate electrons: $Fe^{2+} \rightleftharpoons Fe^{3+}$, this capability makes it useful component of cytochromes, O_2-binding molecules.
- Iron can damage tissues by producing free radicals that attack cellular membranes, proteins, DNA.

Proteins of Iron Transport, Uptake and Storage

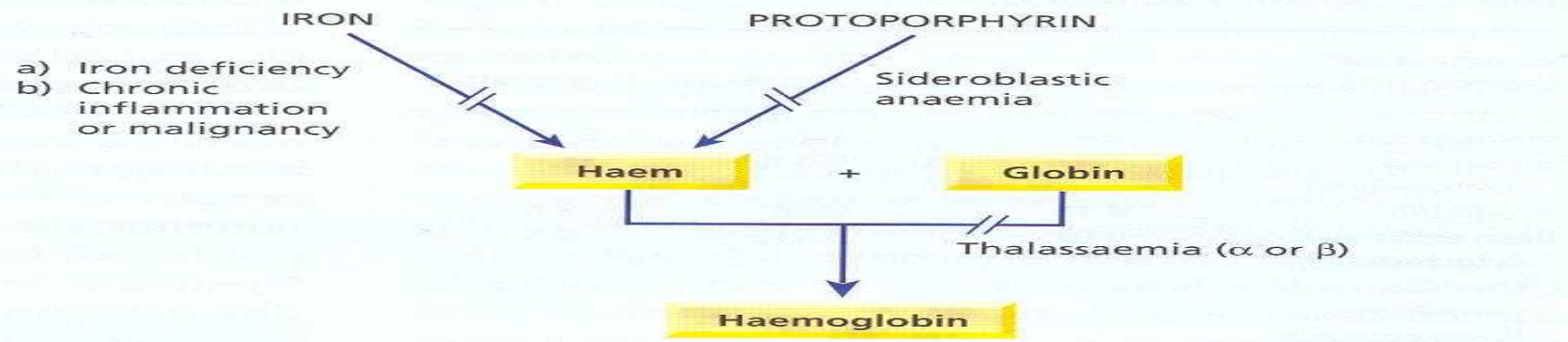
- *Transferrin* – a transport protein, carries iron in the plasma and ECF to supply tissue needs.
- *Transferrin receptor* – a glycoprotein on cell membranes, binds the transferrin-iron complex and is internalized as a vesicle.
- *Ferritin* – iron storage protein.

Proteins of iron regulation

- *Iron Regulatory Proteins* (IRP-1, IRP-2) are mRNA-binding proteins that coordinate expression of transferrin, transferrin receptors and ferritin.
- Hepcidin
- Ferroprotin
- DMT1 (Divalent Metal Transporter - Tranports iron from lumen into the enterocytes)

Iron Metabolism

- Adult man normally have 35-45mg/kg iron, women have less.
- 2/3 of body iron is in haemoglobin in erythron (RBC precursors in the marrow + RBC in blood)
- Most of the remaining iron is found in hepatocytes and reticuloendothelial macrophages which serve as depots


IRON
PROTOPORPHYRIN
a) Iron deficiency
b) Chronic inflammation or malignancy
Sideroblastic anaemia
Haem
+
Globin
Thalassaemia (α or β)
Haemoglobin

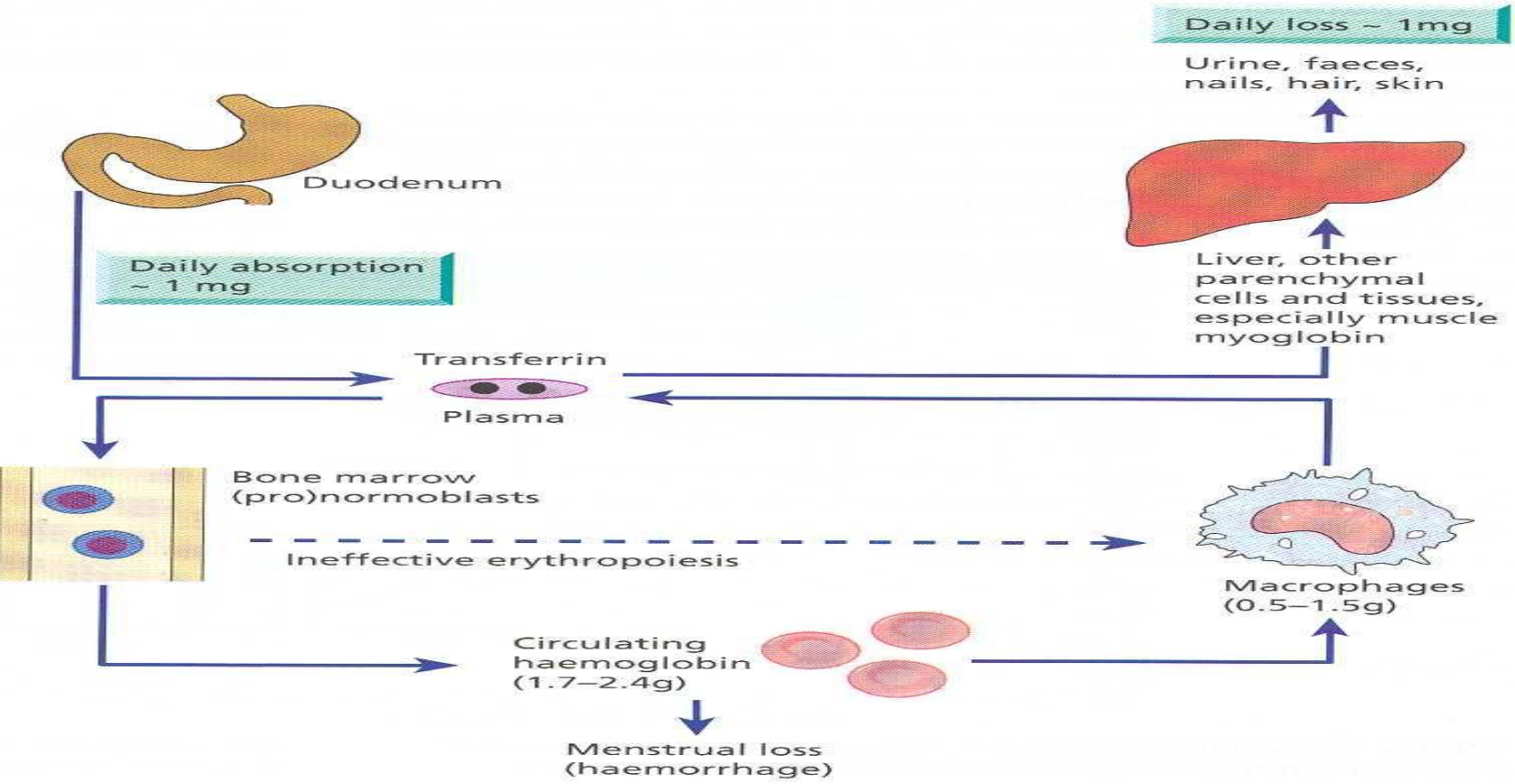

Daily loss ~ 1mg
Urine, faeces, nails, hair, skin
Duodenum
Daily absorption ~ 1 mg
Liver, other parenchymal cells and tissues, especially muscle myoglobin
Transferrin
Plasma
Bone marrow (pro)normoblasts
Ineffective erythropoiesis
Macrophages (0.5–1.5g)
Circulating haemoglobin (1.7–2.4g)
Menstrual loss (haemorrhage)

Table 3.1 The distribution of body iron

Amount of iron in average adult	Male (g)	Female (g)	Percentage of total
Haemoglobin	2.4	1.7	65
Ferritin and haemosiderin	1.0 (0.3–1.5)	0.3 (0–1.0)	30
Myoglobin	0.15	0.12	3.5
Haem enzymes (e.g. cytochromes, catalase, peroxidases, flavoproteins)	0.02	0.015	0.5
Transferrin-bound iron	0.004	0.003	0.1

IRON METABOLISM

- Dietary Iron:

  Iron is essential element and must be precisely regulated.
- On the lumen side of small intestine iron is reduced from its ferric form (Fe^{3+}) to ferrous form (Fe^{2+}).
- Ferrous iron is then transported in enterocytes by DMT1 (divalent metal transporter).

Regulation of Iron Absorption

- *Humans have no physiologic way for iron excretion and regulation of absorption is crucial.*
- The absorption takes place at gastrodeuodenal junction in acid environment.
- There is no role for transferrin in intestinal absorption of iron.
- Hepsidin, Ferriprotin, DMT-1

TRANSPORT PROTEINS

- DMT1 (Divalent Metal Transporter 1)
  (Tranports from lumen into the enterocytes)

- FERROPORTIN1
  (Transports from enterocytes to circulation)

Hepicidin, Primary regulator

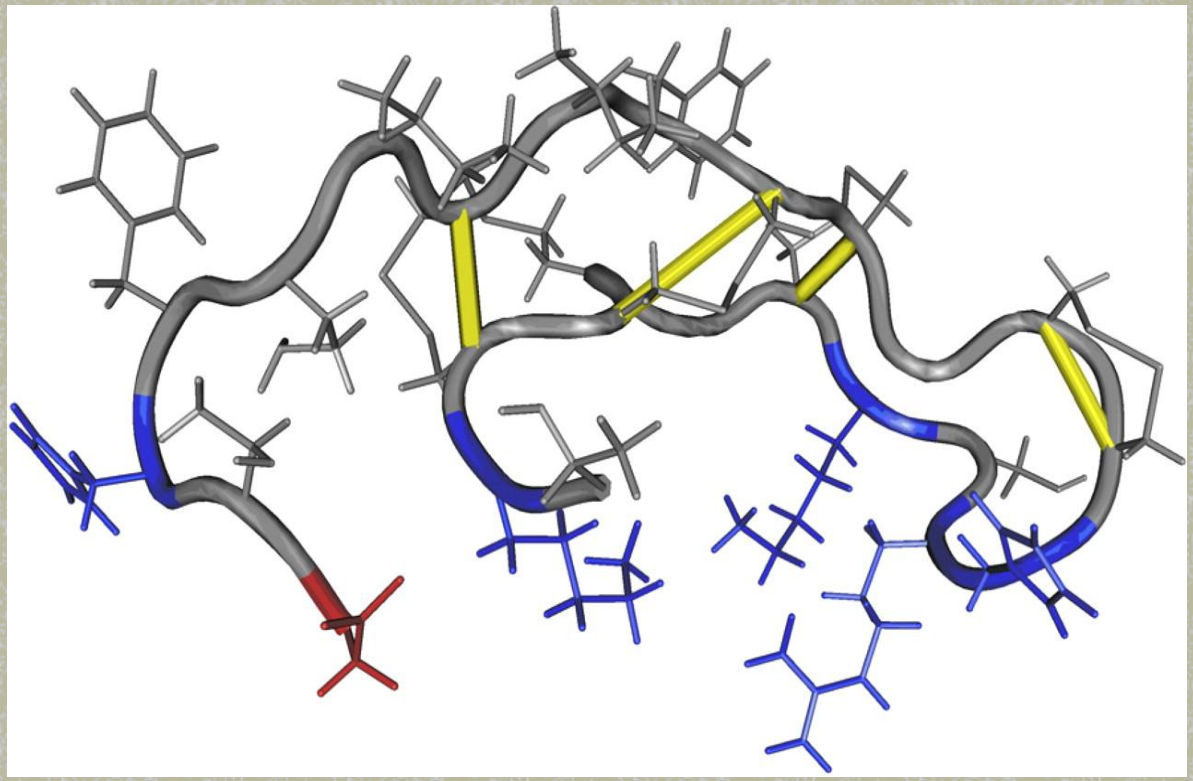
- Increased expression of hepicidin leads to Decrease iron absorption and release.
- Mutation :Hemochromatosis
- Increased expression: Iron deficiency
- Hepicidin mRna expression is increased by erythropoetin, hypoxia & inflammation.
- Also binds to ferroportin.

Hepcidin

- A 25 amino acid polypeptide produced by liver cells
- An acute phase protein
- The major hormonal regulator of iron homeostasis
- Inhibits Fe release from macrophages, intestinal epithelial cells and from placenta
- Interaction with transmembrane Fe transporter *ferroportin* (decrease)
- Inflammatory cytokines *IL-6, TNF* induce hepcidin
- Iron deficiency, hypoxia and ineffective erythropoesis $\longrightarrow$ Decreased hepcidin

HEPICIDN

- 25 Amino acid disulfide peptide.



- Hepcidin lowers iron absorption in the intestine , lowers iron releasing from hepatocytes and macrophages

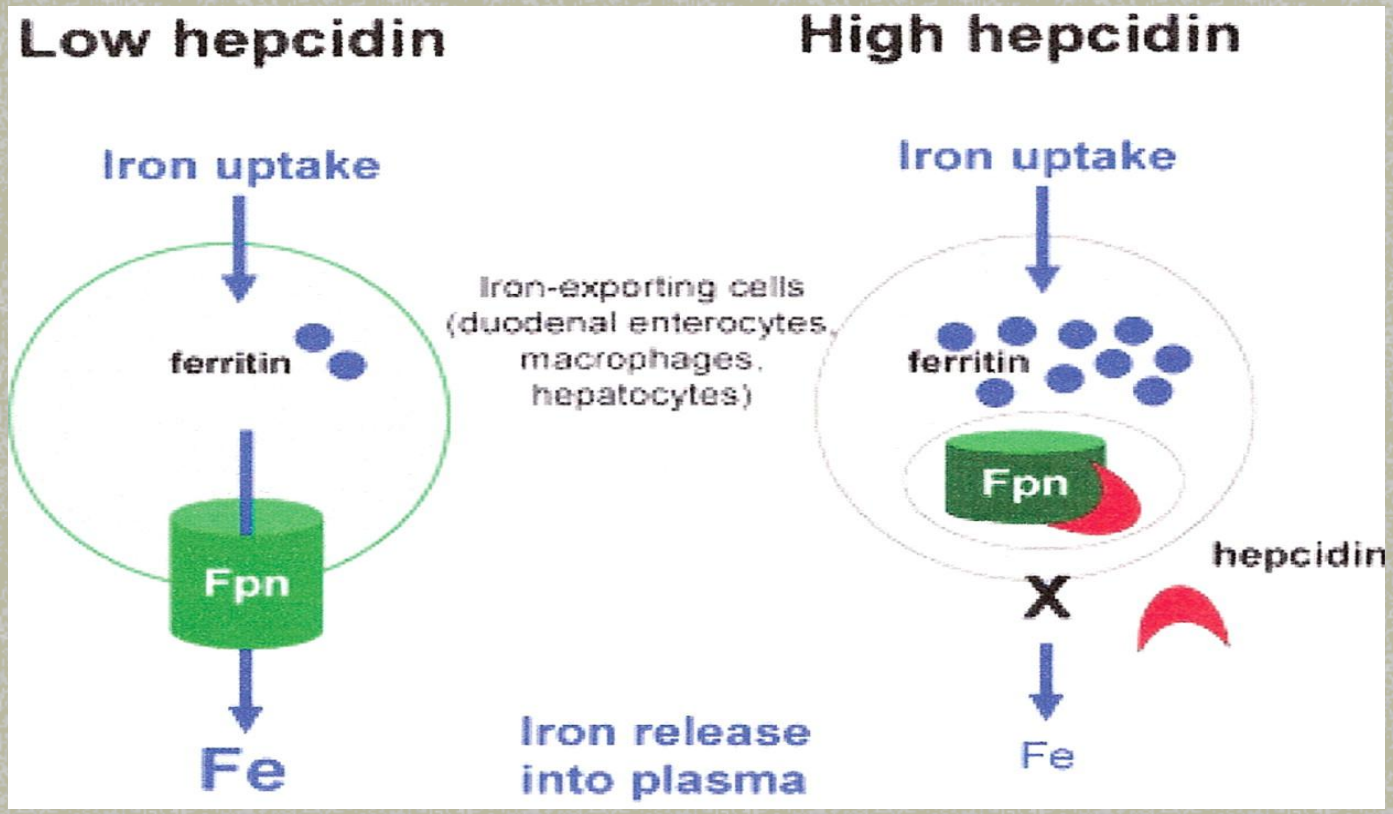
- ⟶ Serum iron is decreased.

Ferroportin

- The only cellular iron exporter in vertebrates.
- Present in macrophages, placenta and the hepatocytes.

Mechanism of action of hepicidin

- The major mechanism of hepicidin is THE REGULATION OF TRANSMEMBRANE IRON TRANSPORT.
- It binds to FERROPORTIN ,forms hepicidin-ferroportin complex ,which is degraded in the lysosomes and iron is locked inside the cells (mainly enterocytes, hepatocytes and macrophages).



Hepicidin Regulation

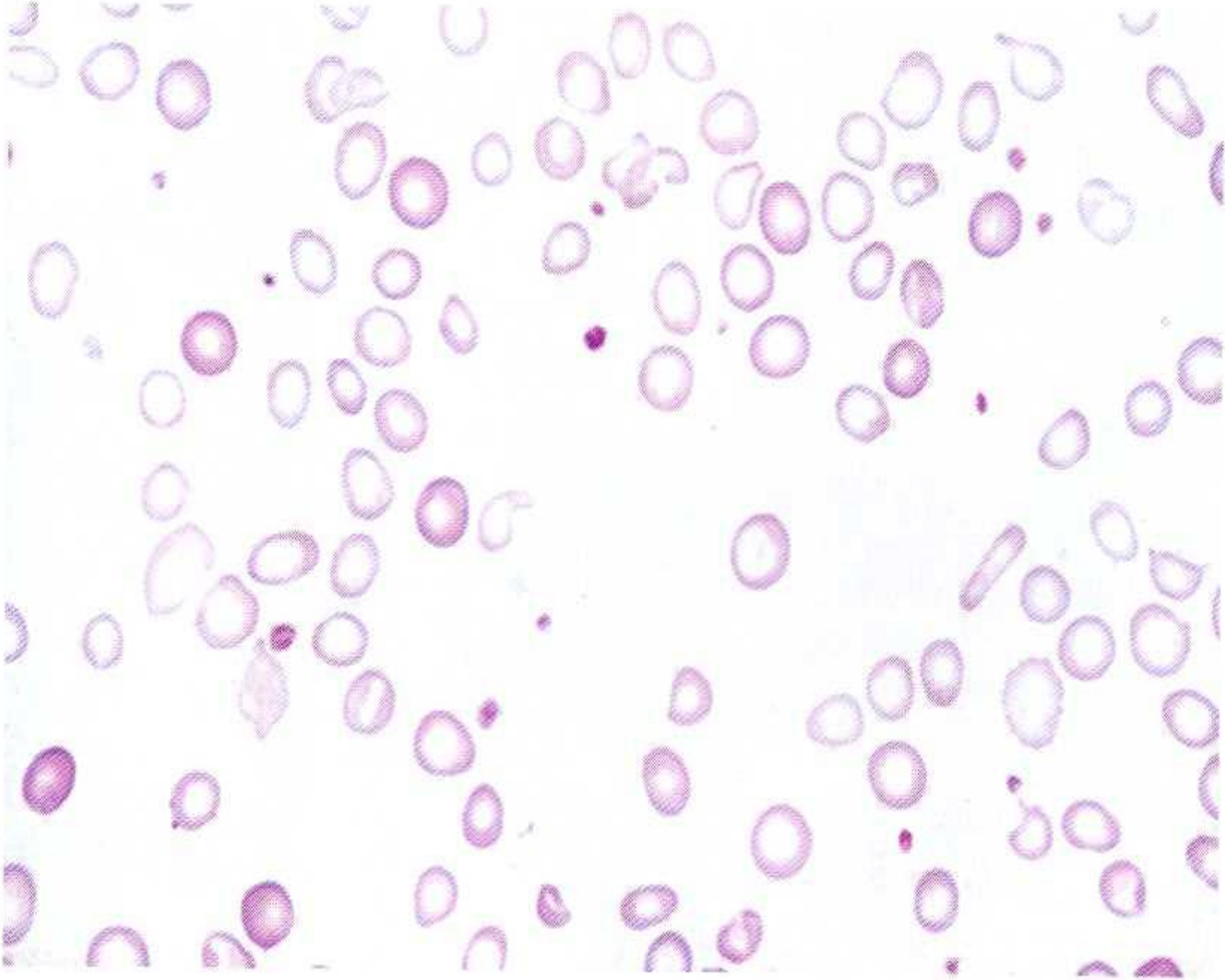
So when hepicidin levels are low ,iron exporting cells have abundant ferroportin and thus releases iron into plasma. When hepicidin concentration increases it binds to ferroportin and thus iron is retained in the .cells

IRON DEFICIENCY

- In 1997 Looker et al reported that 3% of American toddlers, 2-5% of American teenage girls are iron deficient.
- More than half billion people worldwide have adverse effects as a result of iron deficiency.

- **Iron deficiency is the commonest cause of anemia world wild.**

- The anemia of iron deficiency is caused by defective synthesis of hemoglobin resulting in red blood cells that are smaller than normal (*microcytic*), and contain reduced amounts of hemoglobin (*hypo chromic*).



Causes of Iron Deficiency

Inadequate absorption

- Antiacid or high gastric Ph
- Excess bran,phytates
- Loss of enterocytes
- Bowel resection
- Celiac disease
- Inflammatory bowel disease
- Intrinsic RBC defect

Increased loss or requirement

- Growth, pregnancy, lactation
- GIT loss
- Genitourinary loss
- Pulmonary loss
- Other – trauma, excessive phlebotomy, large vascular malformation

Table 3.4 Causes of iron deficiency

Chronic blood loss

Uterine

Gastrointestinal, e.g. peptic ulcer, oesophageal varices, aspirin (or other non-steroidal anti-inflammatory drugs) ingestion, partial gastrectomy, carcinoma of the stomach, caecum, colon or rectum, hookworm, angiodysplasia, colitis, piles, diverticulosis, etc.

Rarely haematuria, haemoglobinuria, pulmonary haemosiderosis, self-inflicted blood loss

Increased demands (see also Table 3.3)

Prematurity

Growth

Pregnancy

Erythropoietin therapy

Malabsorption

For example gluten-induced enteropathy, gastrectomy

Poor diet

A contributory factor in many developing countries but rarely the sole cause except in infants and children

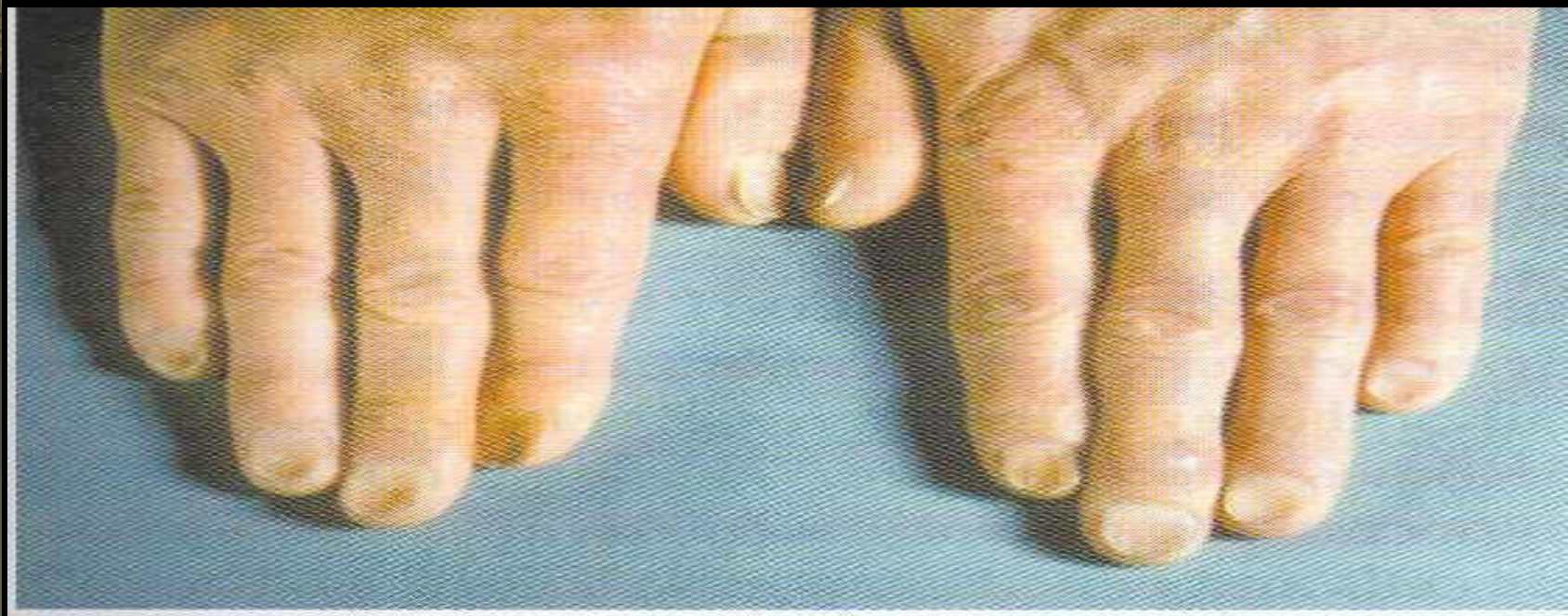
Stages of Iron Deficiency

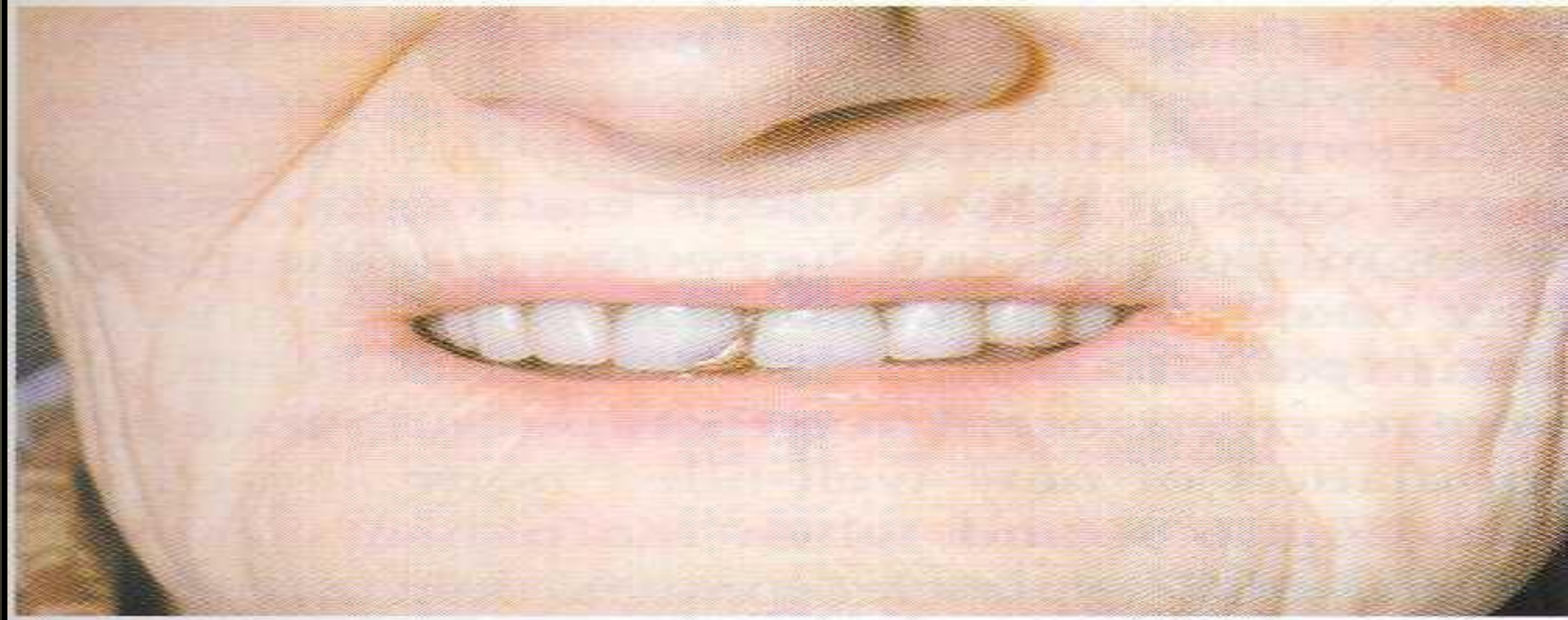
- Iron depletion - decrement of iron stores, no decline in functional iron compound.
- Iron deficient erythropoesis – occurs when iron stores are exhausted and lack.
- Frank Iron Deficiency Anemia.

	Normal	Latent iron deficiency	Iron deficiency anaemia
Red cell iron (peripheral film and indices)	 Normal	 Normal	 Hypochromic, microcytic MCV↓ MCH↓ MCHC↓
Iron stores (bone marrow macrophage iron)	 ++	 0	 0

Clinical Presentation

- Asymptomatic
- Signs and symptoms of underlying disorders
- Manifestations common to anemia from all causes: pallor, weakness, shortness of breath etc.
- Specific to iron deficiency: cognitive abnormalities, pica, koilonychia, blue sclera, Plumer-Vinson syndrome





Laboratory Evaluation

	Fe over load	↑Iron stores	Normal	↓ Fe stores	Fe deplit	Fe def. Eryth	IDA
Trasferrin	<300	<300	330± 30	330-3 60	360	390	410
Ferritin	>250	>250	100± 60	<25	<20	10	<10
Tr. Re	5.5	5.5	5.5± 1.5	5.5	5.5	10	14
Pl. Fe	200	>150	115± 50	<115	<115	<60	<40
Tr. Sat.	>60	>50	35±15	30	<30	<15	<10
RBC	N	N	N	N	N	N	Micro hypo

Table 3.7 Laboratory diagnosis of a hypochromic anaemia

	Iron deficiency	Chronic inflammation or malignancy	Thalassaemia trait (α or β)	Sideroblastic anaemia
MCV MCH	Reduced in relation to severity of anaemia	Normal or mild reduction	Reduced; very low for degree of anaemia	Usually low in congenital type but MCV often raised in acquired type
Serum iron	Reduced	Reduced	Normal	Raised
TIBC	Raised	Reduced	Normal	Normal
Serum transferrin receptor	Raised	Normal/low	Variable	Normal
Serum ferritin	Reduced	Normal or raised	Normal	Raised
Bone marrow iron stores	Absent	Present	Present	Present
Erythroblast iron	Absent	Absent	Present	Ring forms
Haemoglobin electrophoresis	Normal	Normal	Hb A_2 raised in β form	Normal

MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; TIBC, total iron-binding capacity.

Differential Diagnosis of Microcytic Anemias

With decreased iron stores

- Iron Deficiency Anemia

With normal or increased iron stores

- Impaired iron metabolism
- Anemia of chronic disease
- Disorders of globin synthesis: thalassemia
- Disorders of heme synthesis : sideroblastic anemia

THERAPY

- Therapeutic trail of iron – confirms diagnosis of IDA if:
- Reticulocytosis starts 3-5 days from therapy
- Rise of Hb 10-21 days from therapy
- Must make sure – compliance, stop blood loss, treat coexistent disease

ORAL IRON THERAPY

- Ferrous (Fe^{3+}) iron salt supplying 150-200 mg elemental iron daily divided in 3-4 doses
- In children 3mg/kg/day
- Ferrous sulfate most widely used
- Continue treatment for 4-6 months or until ferritin >50µg/l

Parenteral Iron Therapy

- Malabsorption
- Intolerance to oral treatment
- Chronic uncontrolled bleeding
- RISKS – anaphylaxis (0.5-1%), severe serum sickness, given IM – local reactions and staining
- DOSAGE – iron dextrane 50mg/l elemental iron, total dose calculated from iron body deficit to correct Hb, not stores

Suspicion

HYPOCHROMIC MICROCYTIC ANAEMIA

↓

Diagnosis

Low serum iron and ferritin
Raised TIBC and sTfR

↓

Investigation of cause

Female

- Menorrhagia
- Repeated pregnancies

Male or female

- G.I. blood loss
  Occult blood test
  Upper and lower G.I. endoscopy
- Investigation of oth causes (see Table 3.4

↓

Treatment

1. Treat cause
2. Oral iron, e.g. ferrous sulphate to correct anaemia and replenish stores (Rarely parenteral iron)

Iron Overload

Accumulation of iron can occur in disorders associated with excessive absorption or chronic blood transfusions

Disease States

- Hepcidin deficiency, physiological = Haemochromatosis
- Hepcidin excess – anaemia of chronic disease

Table 3.9 The causes of iron overload

Increased iron absorption	Hereditary (primary) haemochromatosis
	Ineffective erythropoiesis, e.g. thalassaemia intermedia, sideroblastic anaemia
	Chronic liver disease
Increased iron intake	African siderosis (dietary and genetic)
Repeated red cell transfusions	Transfusion siderosis

The role of Hepcidin in hereditary hemochromatosis

- Hereditary hemochromatosis:
  -excessive intestinal iron absorption
  -Saturation of transferrin
  -Iron deposition in vital organs

Hereditary Hemochromatosis

- Autosomal recessive disease
- Excessive absorption of Fe from GIT
- HFE – the gene involved, situated close to MHC locus on chromosome 6 and associated with HLA-A3 and –B8
- The consequence of mutation in HFE, it is not expressed on duodenal crypt cells and isn't able to incorporate iron and seems iron deficient and absorbs more iron
- Down regulation of hepcidin

Iron Overload

- ***The clinical features of iron overload from any cause are similar:***

  - skin hyper pigmentation
  - endocrine abnormalities: diabetes mellitus, gonadal, thyroid, pituitary and parathyroid dysfunction
  - liver fibrosis, cirrhosis, hepatocellular carcinoma
  - cardiomyopathy
  - arthropathy

Therapy

- Hemochromatosis without anemia – regular venesection, each unit of blood removes 200-250 mg of iron, with monitoring of Fe, TIBC, Ferritin
- Transfusional iron overload – with Fe chelators that cause to excretion of iron in urine or feces.

Iron chelators

- Deferoxamine – parenteral use, excretion in urine, side effects – deafness, visual, growth, and bone abnormalities
- Deferiprone – oral, 3/d alone or with deferoxamine, urine exretion, more effective in cardiac iron deposition, side effects – arthropathy, agranulocytosis (1%)
- Deferasirox (Exjade) – oral, fecal excretion side effects mild – skin rashes, transient liver enzymes elevation

THANK YOU