Lecture_3

Iron deficiency anaemia

&

anaemia of chronic disease

Fifth year students

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Learning objectives

➢By the end of this lecture, the students would

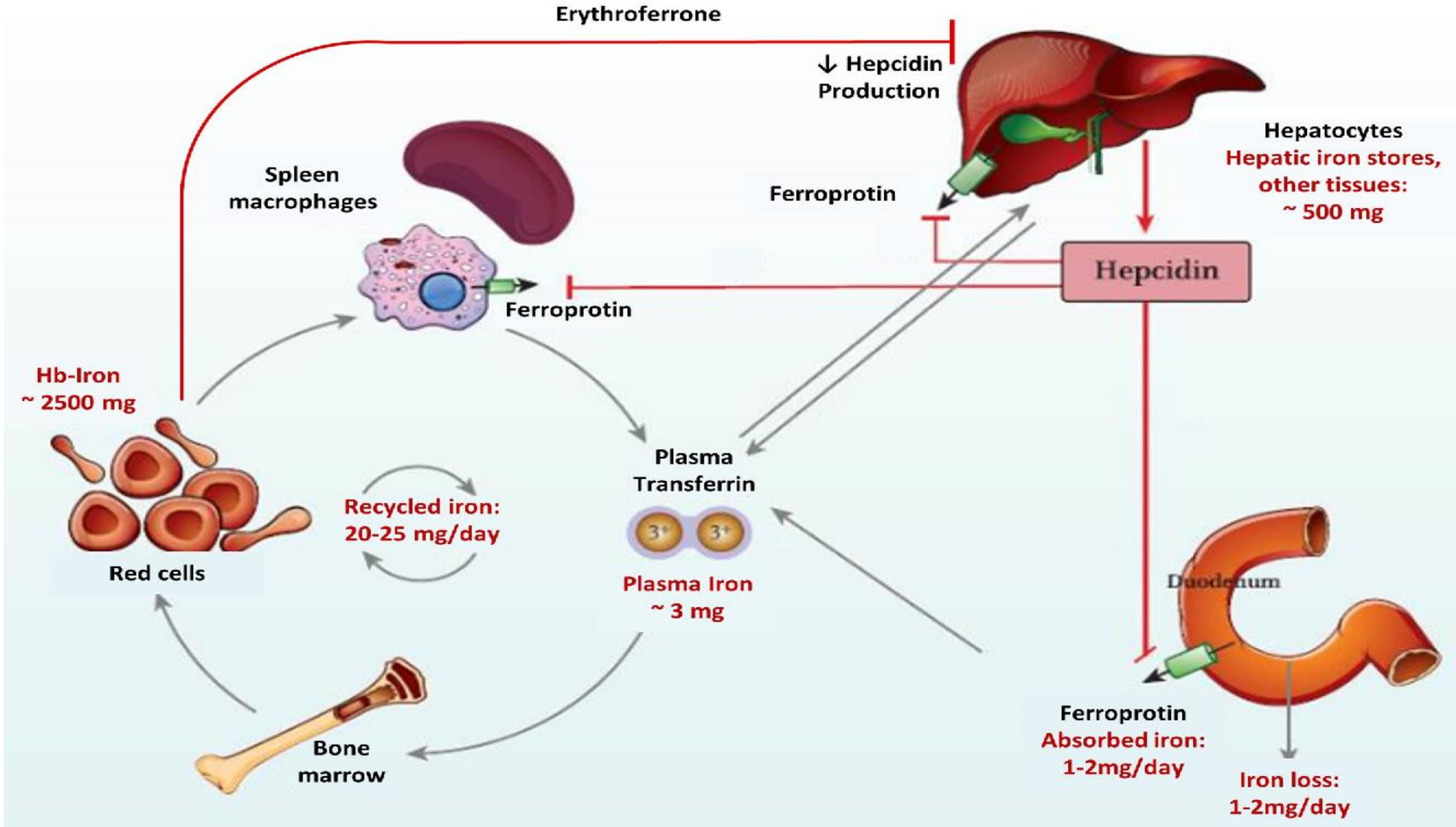
1. Understand and have an idea about the metabolism and the source of body iron
2. Be able to define and recognize Iron deficiency as a cause for anaemia
3. Identify the various reasons for Iron deficiency
4. Have the ability to choose the most appropriate diagnostic test to diagnose IDA and interpret them efficiently
5. Have an idea about the most relevant differential diagnosis of IDA such as anaemia of chronic disease and know how to confirm your diagnosis and how to manage such case

Iron metabolism

- Dietary iron are obtained from heme sources (i.e., meat) and from nonheme sources (e.g., vegetables such as spinach).
- Heme iron is better absorbed than nonheme iron
- In some condition iron absorption can be increased such as: in case of iron deficiency, hypoxia, ineffective erythropoiesis, and hereditary hemochromatosis

- Normally iron is absorbed from the proximal small intestine; it is transported in the cell bound to **ferroportin** and then into the plasma bound to **transferrin**, later transferrin receptor maintain the uptake of iron by the RBC precursors
- Iron absorption from the intestine is further regulated by **hepcidin**, Iron outside Hb-producing cells is stored in ferritin
- The total-body iron conc. in men and women is **50** mg/kg and 40 mg/kg, respectively

- **60% -75%** of the iron is found in Hb
- **2 mg/kg** is found in heme and nonheme enzymes
- **5 mg/kg** is found in myoglobin
- The remainder is stored in **ferritin,** primarily in liver, bone marrow, spleen, and muscle
- The capacity for excreting iron is limited, and iron overload occurs in patients with excessive absorption from the GIT and in those with chronic transfusions
- Iron deposition in endocrine organs, resulting in liver dysfunction, diabetes, and other endocrine abnormalities


Erythroferrone
↓ Hepcidin Production
Hepatocytes
Hepatic iron stores, other tissues: ~ 500 mg
Spleen macrophages
Ferroprotin
Hepcidin
Ferroprotin
Hb-Iron ~ 2500 mg
Plasma Transferrin
Recycled iron: 20-25 mg/day
Red cells
Plasma Iron ~ 3 mg
Duodenum
Bone marrow
Ferroprotin
Absorbed iron: 1-2mg/day
Iron loss: 1-2mg/day

Iron Deficiency Anemia (IDA)

- Iron deficiency is the leading cause of anaemia worldwide
- Although the presentation of classic iron deficiency anaemia is linked with a microcytic anaemia, early iron deficiency is associated with a normocytic anaemia
- Consequently, iron deficiency should be considered in all patients with anaemia, and iron indices should be a part of the evaluation of any patient with hypoproductive anaemia, regardless of the MCV

Causes of IDA

1) Blood loss

- The most common cause for IDA in men and post-menopausal women is gastrointestinal blood loss
- from occult gastric or colorectal malignancy, gastritis, peptic ulceration, inflammatory bowel disease, diverticulitis, polyps and angiodysplastic lesions.
- Worldwide, hookworm and schistosomiasis are the most common causes of gut blood loss
- GI blood loss may be caused by the chronic use of aspirin or NSAIDs, which cause intestinal erosions and impair platelet function

- In women of child-bearing age, menstrual blood loss, pregnancy and breastfeeding contribute to iron deficiency by depleting iron stores

- Menstrual loss (~ 15 mg/month) and (900 mg per pregnancy)

- Very rarely, chronic haemoptysis or haematuria may cause iron deficiency

2) Malabsorption

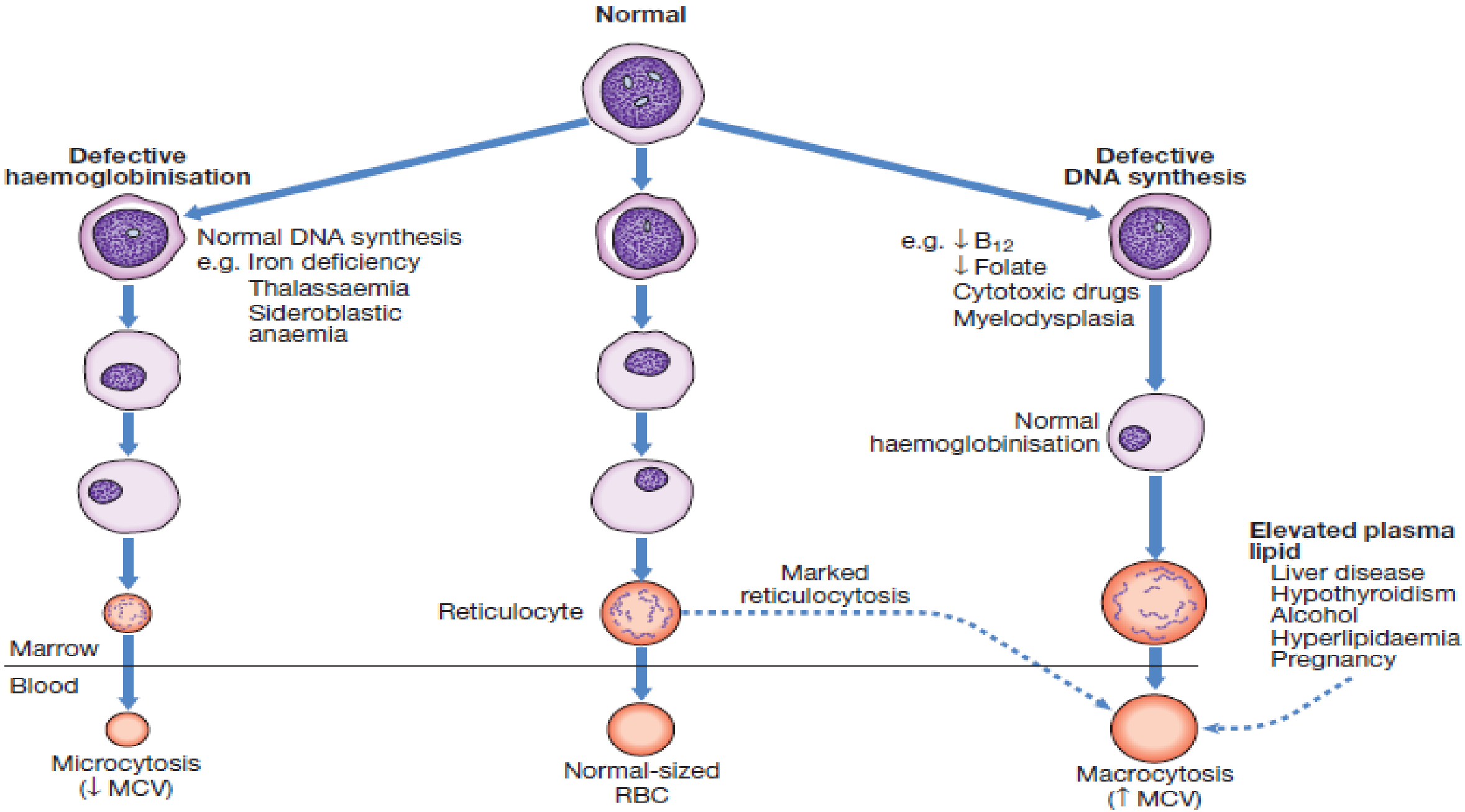
- Normally gastric acid is required to release iron from food and helps to keep iron in the soluble ferrous state
- Achlorhydria (is a state of absent or low hydrochloric acid in the stomach) Occur in the elderly, previous gastric surgery or due to chronic drug use such as proton pump inhibitors that may contribute to the lack of iron availability from the diet
- Iron is absorbed actively in the upper small intestine and hence can be affected by coeliac disease

3. **Helicobacter pylori** infection of gastric or duodenal mucosa causing gastritis and sometimes duodenal ulcer can cause IDA even in the absence of intestinal bleeding

4. **Physiological demands**

Increased iron requirements ex: at times of rapid growth, such as infancy and puberty, which may exceed the usual iron absorption, multiparous women of childbearing age and in babies who drink mostly milk at the expense of an intake of iron containing foods

In pregnancy, iron is diverted to the foetus, the placenta and the increased maternal red cell mass, and is lost with bleeding at delivery


Normal
Defective haemoglobinisation
Normal DNA synthesis
e.g. Iron deficiency
Thalassaemia
Sideroblastic anaemia
Defective DNA synthesis
e.g. ↓ B_{12}
↓ Folate
Cytotoxic drugs
Myelodysplasia
Normal haemoglobinisation
Reticulocyte
Marked reticulocytosis
Elevated plasma lipid
Liver disease
Hypothyroidism
Alcohol
Hyperlipidaemia
Pregnancy
Marrow
Blood
Microcytosis
(↓ MCV)
Normal-sized RBC
Macrocytosis
(↑ MCV)

Investigations

- Confirmation of iron deficiency

1. Serum ferritin

- is a measure of iron stores in tissues
  - It is the best single test to confirm iron deficiency
  - It is a very specific test
  - a subnormal level is due to iron deficiency or, very rarely, hypothyroidism or vitamin C deficiency
  - *Ferritin levels can be raised in liver disease and in the acute phase response*
  - in these conditions, a ferritin level of up to 100 μg/L may still be compatible with low bone marrow iron stores

2) Plasma iron

3) total iron binding capacity (TIBC)

- Both are measures of iron availability; and can be affected by many factors besides iron stores.

- Plasma iron has a marked diurnal and day-to-day variation and becomes very low during an acute phase response but is raised in liver disease and haemolysis

- Transferrin level, the binding protein for iron, are decreased by malnutrition, liver disease, the acute phase response and nephrotic syndrome, but raised by pregnancy and the oral contraceptive pill

4) A transferrin saturation (= iron/TIBC × 100)

- If < 16% is consistent with iron deficiency
- It is less specific than a ferritin measurement
- All proliferating cells express membrane transferrin receptors to acquire iron
- a small amount of this receptor is shed into blood, where it can be detected in a free soluble form

5) Plasma transferrin receptors are blood proteins, may be elevated in persons with IDA

When there is low Iron store:

- Up-regulation transferrin receptors
- Increase in the levels of soluble plasma transferrin receptors

- Elevated levels are seen in IDA
- Decreased transferrin receptor levels are seen in the following:
  - Iron overload
  - Protein malnutrition
  - Atransferrinemia (genetic absence of transferrin receptor)

Investigation of the cause This depends on:

- The patients' characteristics (age and sex)
- Hx and clinical findings

- In men and in post-menopausal women with a normal diet, the upper and lower GIT should be investigated by endoscopy or radiological studies
- Serum anti-transglutaminase antibodies and a duodenal biopsy are required to diagnose coeliac disease
- In the tropics, stool and urine should be examined for parasites
- In difficult cases, it may still be necessary to examine a bone marrow aspirate for iron stores

Management

- Blood transfusion is not manditary and oral iron replacement is appropriate, except in certain situation:
    - patient has angina
    - heart failure
    - evidence of cerebral hypoxia

- Ferrous sulphate 200 mg 3 times daily (195 mg of elemental iron per day) is adequate and should be continued for **3–6** months to replete iron stores
- side-effects include: GI upset as *dyspepsia and altered bowel habit* which can be improved by reducing the dose to 200 mg twice daily or a switch to **ferrous gluconate** 300 mg twice daily (70 mg of elemental iron per day) or another alternative oral preparation should be tried.

- Delayed-release preparations are not useful, since they release iron beyond the upper small intestine, where it cannot be absorbed.
- The aim of treatment is to raise Hb by~**10 g/L** every 7–10 days and a reticulocyte response will be evident within a week
- A failure to respond adequately may be due to
  - non-adherence
  - continued blood loss
  - malabsorption or an
  - incorrect diagnosis
- Patients with malabsorption, chronic gut
- disease or inability to tolerate any oral preparation may need
- parenteral iron therapy.

- Previously, iron dextran or iron sucrose was used, but new preparations of iron isomaltose and iron carboxymaltose have fewer allergic effects and are preferred.
- Doses required can be calculated based on the patient’s starting haemoglobin and body weight
- Observation for anaphylaxis following an initial test dose is recommended.

Anaemia of chronic inflammation (AI)

previously known as anaemia of chronic disease (ACD)

is a common type of anaemia, particularly in hospital populations.

- occurs in patients with chronic inflammatory, infectious, malignant, or autoimmune disorders.
- Anaemia is not related to bleeding, haemolysis or marrow infiltration
- Usualy is mild, with
- Hb in the range of 85–115 g/L, with a normal MCV (normocytic, normochromic
- The serum iron is low but iron stores are normal or increased

Pathogenesis

- Hepcidin is a key regulatory protein that the development of ACD/AI it is produced by the liver in response to pro-inflammatory cytokines, especially IL-6,TNF and interferon
- Hepcidin binds to ferroportin on the membrane of iron-exporting cells, such as small intestinal enterocytes and macrophages, internalising the ferroportin and thereby inhibiting the export of iron from these cells into the blood
- The iron remains trapped inside the cells in the form of ferritin, levels of which are therefore normal or high in the face of significant anaemia
- Inhibition or blockade of hepcidin is a potential target for treatment of this form of anaemia

Diagnosis and management

- We should distinguish ACD with a low MCV from IDA
- BM examination may ultimately be required to assess iron stores directly
- In difficult situations a trial of oral iron can be used (positive response occurs in true IDA but not in ACD).
- Treating the underlying disorder generally help to improve the ACD
- Trials of higher-dose intravenous iron are under way to try to bypass the hepcidin-induced blockade.

Investigations to differentiate AI from IAD

	Ferritin	Iron	TIBC	Transferrin saturation	Soluble transferrin receptor
IDA	↓	↓	↑	↓	↑
AI	↑/Normal	↓	↓	↓	↓/Normal

Questions:

1) A 32 year old man was found to have a Hb of 7.8 gm/dL with reticulocyte count of 0.8%. B. film showed microcytic hypochromic anaemia. Hb A2 and Hb F levels were 2.4% and 1.3% respectively. Serum iron and TIBC were 15 mgm/dL and 420 mgm/dL respectively. The likely diagnosis is:
    1) a. IDA
    2) b. β thalassemia minor
    3) c. Sideroblastic anaemia
    4) d. Anaemia of chronic inflammation
2) Which of the following test is best in differentiating between anaemia of chronic inflammation and IDA?
    1) a. Serum ferritin
    2) b. Serum transferrin receptor
    3) c. TIBC
    4) d. Transferrin saturation

Thank you