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Iron deficiency: clinical pathology and treatment

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A recent metadata study in THE LANCET (https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)32594-0.pdf) highlights the tremendous burden of disease of iron deficiency anaemia.

Children, premenopausal and pregnant women, and people in low-income and middle-income countries are particularly vulnerable.

Iron deficiency occurs when either total iron stores are low (insufficient intake, excessive loss usually via bleeding) or when inflammation blocks the release of iron into the plasma (effected by the major iron metabolic regulator, hepcidin).

Plasma is the route via which iron reutilisation is facilitated (fig 1), with a typical 70kg adult male having a total iron content of between 3.5 and 4.5g. This typical scenario can be misleading of course, because the 'normal' iron requirements and concentrations vary greatly depending on the individual (e.g., children and pregnant women have far greater iron requirements).

Clinical pathology

When a simple, uncomplicated iron deficiency is suspected a serum ferritin level is adequate.

This must, however, always be interpreted in conjunction with the clinical context e.g., pregnancy, age, premenopausal etc, as the reference ranges will vary.

When there are co-morbidities, full iron studies are indicated, especially when there is concomitant inflammation or chronic disease. Ferritin is an acute phase reactant and increases non-specifically.

Furthermore, conditions that lead to cell damage, especially cell necrosis in the liver can lead to a huge spike in ferritin due to the release from hepatocytes.

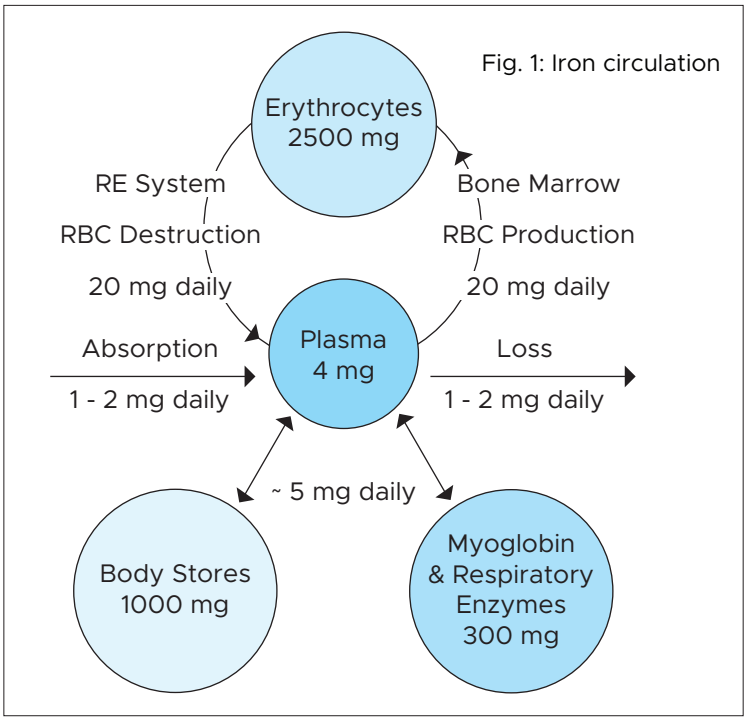

Fig. 1: Iron circulation

As an aside, it is noted that ferritin can be markedly increased in acute SARS-CoV2 infections often reaching levels above 1000ng/ml.

The reason for this is not entirely clear, although the link with elevated IL-6 and inflammation is assumed. Table 1 represents the common iron study results in different scenarios.

Clinical presentation

The clinical presentation of iron deficiency anaemia is very variable. The typical signs and symptoms may include extreme fatigue and weakness, pallor, chest pain, tachycardia, shortness of breath, headache, dizziness, cold peripheries, glossitis, brittle nails, unusual cravings for non-nutritive substances (e.g., ice, sand), poor appetite etc.

In children or the elderly, the presentation can be quite atypical, e.g., for children difficulty concentrating at school is likely and in the elderly depression is common.

Table 1: Iron studies in three potential scenarios

	IRON DEFICIENCY	ANAEMIA OF CHRONIC DISEASE	IRON OVERLOAD
Mean cell volume	Low	Low or normal	Normal
Serum iron	Low	Low	High
TIBC / transferrin	High	Low or normal	Low
Transferrin saturation	Low	Low	High
Serum ferritin	Low	Normal or high	High
Bone marrow iron stores	Low	High	High
Red cell distribution width	High	Normal or high	Normal

Iron regulation and metabolism

Hepcidin lies at the centre of iron regulation. It is not only an iron-regulatory hormone, but it is also important in inflammation where hepcidin synthesis is markedly increased.

This is independent of iron status and increased iron uptake and inhibition of release into the plasma is a side-effect. Hepcidin synthesis is induced (+) by iron loading and inflammation and inhibited (-) by erythropoietic activity (Fig 2).

Increased hepcidin levels limit iron absorption from the gut and the release of iron stores from the liver and reticuloendothelial system.

In cases of chronic inflammation, elevated hepcidin leads to similar events and the characteristic anaemia of chronic disease.

Suppressing hepcidin production increases iron availability by enhancing gastrointestinal absorption and the release of iron stores from the liver and the reticuloendothelial system.

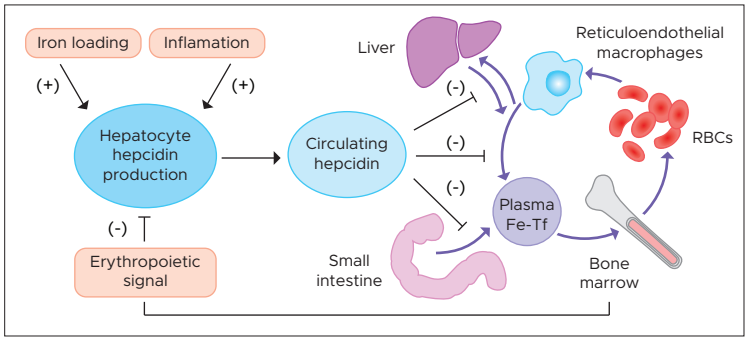

Fig 2. The central role of hepcidin.
From "Iron transport proteins: Gateways of cellular and systemic iron homeostasis" by M.D. Knutson, JBC, 292. 2017).

Recommendations for treatment

Oral iron therapy is usually the first line of treatment in most cases. It should be remembered, however, that upregulation of hepcidin by high dose iron supplementation limits absorption efficiency so it is sometimes better to use lower doses over longer periods.

Parenteral iron formulations (e.g., Ferinject) have substantially altered replacement therapy and enable rapid, safe total-dose iron replacement. Total iron replacement required can be calculated with reasonable accuracy. Box 1 provides an example of how this is done. Unless a clear dietary deficiency is identified, underlying causes should be considered, for example, blood loss via the GIT or UGT. Screening for coeliac disease may be helpful, especially in cases where blood loss is not identified and there is little or no response to iron supplementation (RIDA: refractory iron deficiency anaemia). Genetic and other causes of refractory iron deficiency occur, but these are rare and investigated as a last resort.

Box 1 - Parenteral iron replacement.

1. Intravenous iron formulations have altered replacement therapies dramatically.
2. A test dose should always be administered initially to ensure no adverse reactions.
3. Product labels specify the dose and replacement.
4. There are several online iron replacement calculators (e.g., https://www.calculosaurus.com/ferinject-dose-calculator). These can be used to corroborate one's own calculation using the Ganzoni formula and the product label suggestions.
5. A patient's total body iron deficit can be calculated using the Ganzoni formula (total iron dose replacement = [actual body weight × (target Hb - actual Hb)] × 2.4 + iron stores). The depot iron stores depend upon weight. For children <35kg the target iron stores are 15mg/kg. For individuals >35kg the depot iron store is ~500mg.
6. Administration is usually via one or two (1 week apart) doses.
7. Follow up Hb, red cell parameters and iron studies are indicated after 1 week of the intravenous transfusion.