Non-anaemic Iron Deficiency

Iron deficiency is a reduced content of total body iron. Iron-deficiency anaemia (IDA) occurs when the iron deficiency is sufficient to reduce erythropoiesis and therefore the haemoglobin (Hb) level falls. However, problems related to iron depletion can develop before this stage. Globally, iron deficiency is the most common cause for anaemia[1].

Non-anaemic iron deficiency (NAID) is sometimes termed 'latent iron deficiency' or 'depleted iron stores'[2]. To avoid confusion in this article, non-anaemic iron deficiency will be referred to as 'iron depletion'.

There is a separate Iron-deficiency Anaemia article.

Epidemiology

Iron depletion may be three times as common as iron deficiency anaemia (IDA), which has a prevalence of 2-5% of adult men and postmenopausal women in the developed world[3]. Iron depletion is more common in the developing world[4].

Risk factors

- Iron deficiency is common in children and adolescents[5].
- Iron deficiency is relatively common in the elderly population[6].
- Women of childbearing age are most at risk of iron deficiency due to losses in menstruation and pregnancy[7]. Iron deficiency may be an under-recognised cause of fatigue in women of childbearing age[8].
- Obesity is also a risk factor for iron deficiency[9]. The mechanism is not fully understood, but may involve reduced absorption of iron from the upper GI tract, increased requirements and/or the impact of obesity-related inflammation.

Physiology[1, 7]

- Iron balance is regulated by absorption of iron rather than by excretion, because humans cannot actively excrete iron. Iron is absorbed from the small intestine.
- Dietary iron is in one of two main forms, haem iron (the organic form, mainly found in meat) and non-haem or free iron (the inorganic form, mainly from plants). Haem iron is more easily absorbed. Non-haem iron may be in ferrous or ferric form. Ferrous iron can be absorbed directly by the intestinal cells; ferric iron has to be converted before it can be absorbed. Non-haem iron absorption can be improved by meat and ascorbic acid (vitamin C). Absorption is inhibited by calcium, phytates (in some plant foods) and polyphenols (in tea and coffee). If iron is not required by the body it is stored by the iron storage protein ferritin. If needed it is converted to ferrous iron and transported in the circulation bound to transferrin.
- The regulation of iron absorption and transport is complex; there seems to be an important role for hepcidin, a hormone secreted by the liver. Hepcidin has an effect on the transfer of iron into plasma from enterocytes, hepatocytes and macrophages.
- Iron is lost from the body through sloughed skin cells and sloughed enterocytes from the gut, and through any form of blood loss.
- A mature fetus has iron stores, which are required because breastfeeding does not meet the infant's iron requirements. Low birth-weight babies lack this store.
- Iron requirements increase at times of growth (early childhood and adolescence); during pregnancy and with menstruation.
- Iron is present in many foods, so iron intake per se is partly related to overall calorie intake, although subsequent absorption and metabolism are affected by many variables.

Aetiology[5]

Inadequate intake (nutritional iron deficiency):

- Plant-based diets with little meat.
- Low calorie intake in relation to iron requirement - eg, growing children, pregnant women and the elderly.

Inadequate absorption:

- Malabsorption - eg, coeliac disease.
- Excessive consumption of foods which reduce absorption - eg, cow's milk, tea.
- Achlorhydria (gastric acid maintains ferric iron in solution, so aids absorption) - eg, from proton pump inhibitors or post-gastrectomy.
- Helicobacter pylori colonisation (possibly) reduces iron uptake.

Excessive loss:

- Menorrhagia.
Gastrointestinal (GI) losses:
- Peptic ulcer, erosion, oesophagitis.
- GI malignancy (although this tends to cause iron deficiency with anaemia)\(^3\).
- Inflammatory bowel disease.
- Coeliac disease.
- Non-steroidal anti-inflammatory drugs (NSAIDs).
- Other GI losses - eg, recurrent bleeding from haemorrhoids, dental bleeding or epistaxis.
- Intestinal parasites - eg, hookworms.

- Exfoliating skin conditions.
- Haematuria.
- Blood donation.
- Intravascular haemolysis (rarely).
- Endurance athletes may be at risk of iron depletion from increased losses.

Functional iron deficiency:
- This is inadequate iron supply to the bone marrow, while storage iron is present in the reticulo-endothelial cells.
- It can occur in chronic kidney disease (CKD) and many chronic inflammatory diseases (eg, rheumatoid arthritis and inflammatory bowel disease)\(^3\),\(^10\).
- Iron deficiency can be either absolute or functional in patients with heart failure, and is an independent predictor of outcomes and significantly contributes to exercise intolerance, whether there is anaemia or not. It may be caused by blood loss due to medication (anti-platelets, anticoagulants), malabsorption or reduced intracellular iron uptake\(^10\). Patients with heart failure should be screened for iron level even if they are not anaemic, as treatment of depletion can improve prognosis\(^11\).

Presentation

Symptoms
There may be no symptoms until significant anaemia develops. Symptoms which may be linked to iron depletion are\(^5\):
- Fatigue\(^12\).
- Poor work productivity.
- Poor attention and memory.
- Sore tongue.
- Poor condition of skin, nails or hair, including hair loss.
- Delayed skin wound healing\(^13\).
- Developmental delay.
- Restless legs syndrome\(^14\).

Signs
There may be no signs. Possible signs of iron depletion (although more usually seen in IDA) are:
- Angular cheilitis or angular stomatitis.
- Atrophic glossitis.
- Nails which may show brittleness, ridging or koilonychia (spoon-shaped nails).
- Poor condition of skin or hair.

Investigations\(^15, 16\)

Initial investigation of iron status
FBC and serum ferritin are the most useful initial tests for iron depletion in most people.

FBC may show:
- Microcytosis - reduced mean cell volume (MCV) - and hypochromia - reduced mean cell haemoglobin (MCH). MCH is the more reliable of these two. Note that MCH and MCV are affected by vitamin B12 or folate deficiency.
- Increased red cell distribution width (RDW).
- Hb level is required to exclude anaemia.

Interpretation of ferritin levels
- Ferritin levels reflect body iron stores in otherwise healthy people. Serum ferritin assay has become the standard test for the assessment of iron stores.
- However, ferritin levels are unreliable in:
  - Acute or chronic inflammation. Simultaneously checking another inflammatory marker such as ESR or CRP may help to establish if inflammation could be a confounding factor in interpreting ferritin.
  - CKD.
  - Heart failure.
  - Liver disease.
  - Excessive alcohol intake.
Further investigation of iron status

Where the diagnosis is unclear the following may be helpful:

- Discussion with a haematologist.
- Blood film.
- Vitamin B12 and folate levels.
- Tests for other causes of fatigue, microcytosis, inflammation, etc:
  - Hb electrophoresis (for haemoglobinopathies).
  - TFTs.
  - Liver and renal function.
  - Inflammatory markers: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

- Other tests of iron status:
  - Reticulocyte haemoglobin content: an early indicator of iron depletion, but not always available; gives false normal values in some situations - eg, thalassaemia and high MCV.
  - Other serum markers of iron depletion are: low serum iron, low transferrin saturation, high transferrin receptor levels, raised iron-binding capacity, high percentage of hypochromic red blood cells, and raised red cell protoporphyrin.
  - In chronic disease a more helpful measure may be the ratio of serum transferrin receptors/log 10 serum ferritin.$^3$
  - Bone marrow biopsy: can assess iron status and look for other causes of abnormal blood picture - eg, myelodysplasia.
  - Therapeutic trial of iron. If iron deficiency is likely but is difficult to confirm - eg, in the presence of chronic disease - it may be appropriate to try iron therapy and repeat blood tests after a few weeks.

- Pregnancy:
  - The MCV may naturally increase by approximately 4 fL.
  - In the 2nd-3rd trimester, if iron levels need to be assessed, the most helpful indicators are erythrocyte protoporphyrin levels or transferrin receptors. Ferritin levels, serum iron and transferrin are not useful in this scenario.

- CKD:
  - There are specific National Institute for Health and Care Excellence (NICE) guidelines for assessment of iron status in CKD.$^{17}$ In this scenario, ferritin or transferrin saturation alone should not be used to assess iron deficiency status. Ideally, percentage of hypochromic red blood cells (% HRC) is measured, but if this is not possible (the sample has to be processed within six hours) then reticulocyte Hb content or equivalent may be used.

Investigating the cause of iron imbalance

It is less certain who needs investigating in iron depletion, but the following information may be relevant:

- Coeliac disease is common and easily missed. Some authors state that coeliac disease may also manifest as iron depletion.
- The British Society of Gastroenterology guidelines comment that, on current evidence, the prevalence of GI malignancy is low in patients with iron depletion. They suggest that, from the available evidence, only postmenopausal women and men >50 years require GI investigation for iron depletion.$^3$
- Diets which are borderline low in iron are common.
- If the blood picture does not improve with treatment - eg, a trial of iron therapy - then evaluate further. See 'Iron therapy', below.

Differential diagnosis

Other causes of a similar blood picture (microcytosis and hypochromia) are:

- Haemoglobinopathies - eg, thalassaemia, sickle cell disease.
- Hypothyroidism.
- Anaemia of chronic disease (but iron-deficiency can co-exist).
- Myelodysplastic disorders.

Management

The aims of treatment are to restore red cell indices to normal, to replace iron stores and to treat any underlying cause. There is no consensus about treatment in the absence of anaemia, but there is evidence for some degree of symptomatic improvement, particularly for fatigue.$^{12}$ Iron supplementation is often associated with side-effects, so it makes sense to treat those who are symptomatic, and monitor all for development of anaemia.$^7$

Where diet is a factor, nutritional advice may be helpful. Regular consumption of haem iron (eg, red meat, poultry, fish) five times a week along with regular non-haem iron in the form of green vegetables, etc, is recommended.$^7$
Iron therapy

- Ferrous iron salts:
  - Ferrous sulfate 200 mg twice daily is simple and inexpensive.
  - Ferrous fumarate, ferrous gluconate or iron suspensions may be better tolerated than ferrous sulfate.
  - Common side-effects are nausea and epigastric pain. These may be reduced by taking the iron with meals or reducing the dose. Constipation or diarrhoea may also occur.
  - Lower doses of ferrous sulfate may be better tolerated and equally effective.
  - Iron supplements taken every few days may also be effective[9].
  - Keep iron preparations out of children’s reach.

- Ascorbic acid 250-500 mg twice daily, taken with the iron, enhances absorption.
- High hepcidin levels block absorption of oral iron in inflammatory disorders [18].
- Parenteral iron preparations may be indicated where oral iron is not tolerated or absorbed. Side-effects and serious adverse reactions are possible.
- There are separate guidelines for treating iron deficiency in CKD [17]. This involves the use of erythropoietic stimulating agents and/or oral or intravenous iron therapy. For more information, see the separate Anaemia in Chronic Kidney Disease article.

Complications

- Iron depletion may cause fatigue and reduced work performance.
- Iron depletion may affect cognitive or motor development in children. However, the evidence is equivocal.
- Iron depletion may affect immune function.
- Iron depletion may increase the risk of developing heart failure, and seems to adversely affect prognosis of existing heart failure [19].
- The risk of chronic lead poisoning may be increased by iron depletion.
- Iron overload can result from excessive replacement, and there can be a secondary haemochromatosis [7].

Prognosis

Iron therapy should resolve the symptoms, signs and blood picture, unless there is a serious underlying cause. The depletion is likely to recur unless the cause is addressed.

Prevention

- Adequate diet. This may be augmented by:
  - Taking vitamin C (or foods rich in it) with meals.
  - Avoiding excess consumption of foods inhibiting iron absorption - eg, tea and coffee, cow’s milk.
  - For babies, breastfeeding and a suitable weaning diet.

- Treatment of intestinal parasite infections.
- Routine iron supplementation (particularly for women of childbearing age) or fortification of foods is feasible. However, untargeted iron supplementation may have adverse effects; its benefits and harms are debated [4].

Further reading & references

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- Guidelines for the management of iron deficiency anaemia; British Society of Gastroenterology (March 2011)
15. Anaemia - iron deficiency; NICE CKS, February 2013 (UK access only)
16. Guideline for the laboratory diagnosis of functional iron deficiency; British Committee for Standards in Haematology (May 2013)
17. Anaemia management in people with chronic kidney disease; NICE Guidelines (June 2015)

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