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.

Note that most of the literature on this topic deals with *iron deficiency anaemia* and there is less information on iron depletion with normal haemoglobin levels.

Non-anaemic iron deficiency is sometimes termed 'latent iron deficiency' or 'depleted iron stores'.[1] To avoid confusion in this article, non-anaemic iron deficiency will be referred to as 'iron depletion'.

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.[2] Iron depletion is more common in the developing world.

Physiology[3]

- 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.
- The regulation of iron absorption and transport is complex; there seems to be an important role for hepcidin, a hormone secreted by the liver.
- 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 breast-feeding does not meet the infant's iron requirements. Low birthweight babies lack this store.
- Iron requirements increase at times of growth (early childhood and adolescence); during pregnancy and with menstruation.
- Dietary iron is in two forms, haem iron (the organic form, mainly found in meat) and non-haem iron (the inorganic form, mainly from plants). Haem iron is much better 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).
- Iron is present in many foods, so iron intake is partly related to calorie intake.

Aetiology[3]

Inadequate intake (nutritional iron deficiency):

- Monotonous 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 cows' 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*[2]).
    - Inflammatory bowel 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,[4] but iron supplementation for athletes is debated and indiscriminate supplements could be harmful.[5]

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 renal failure.[2]

Presentation

Symptoms

There may be no symptoms until significant anaemia develops. Symptoms which may be linked to iron depletion are:[3]

- Fatigue.[6]
- Poor work productivity.
- Poor attention and memory.
- Sore tongue.
- Poor condition of skin, nails or hair, including hair loss.
- Pica (there has been debate as to whether pica is the cause or the result of iron and zinc deficiency).[7]
- Developmental delay (see below).
- Restless legs syndrome.[8]

Signs

There may be no signs. Possible signs of iron depletion (although more usually seen in iron deficiency anaemia (IDA)) are:

- Angular cheilitis or angular stomatitis.
- Atrophic glossitis.
- Nails may show brittleness, ridging or koilonychia (spoon-shaped nails).
- Poor condition of skin or hair.

Investigations

Initial investigation of iron status[9]

FBC and serum ferritin are the most useful initial tests for iron depletion.

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.
- However, ferritin levels are unreliable in:[3] acute or chronic inflammation, chronic kidney disease (CKD), heart failure,[10] liver disease, malignancy and hyperthyroidism.

With iron depletion, there is less information about ferritin levels in the literature. One study suggests that, in otherwise healthy people, ferritin levels of <22 µg/L could be used to define clinically relevant iron storage depletion (this includes the pre-anaemic stages of iron deficiency).[11]

Further investigation of iron status [9] [12]

Where the diagnosis is unclear the following may be helpful:

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

- Other tests of iron status:[1]
    - 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[11], raised iron-binding capacity, and raised red cell protoporphyrin.
    - In chronic disease a more helpful measure may be the ratio of serum transferrin receptors/log 10 serum ferritin.[2]
    - 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:[13]
    - 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 separate guidelines for assessment of iron status in CKD.[14]

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.[15]
- The British Society for Gastroenterology guidelines comment that, on current evidence, the prevalence of gastrointestinal (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.[2]
- Diets which are borderline low in iron are common.
- If the blood picture does not improve with treatment, eg a trial of iron therapy - see 'Iron therapy' below, then evaluate further.

Differential diagnosis

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

- Haemoglobinopathies.
- Hypothyroidism.
- Anaemia of chronic disease (but iron-deficiency can coexist).[3]
- 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.

Iron therapy[2]

- Ferrous iron salts:
    - Ferrous sulphate 200 mg twice daily is simple and inexpensive.
    - Ferrous fumarate, ferrous gluconate or iron suspensions may be better tolerated than ferrous sulphate.
    - 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 sulphate may be better tolerated and equally effective.
    - Iron supplements taken every few days may also be effective.[3]
    - Keep iron preparations out of children's reach.
- Ascorbic acid 250-500 mg twice daily, taken with the iron, enhances absorption.
- Parenteral iron preparations are rarely indicated. Side-effects and serious adverse reactions are possible.
- There are separate guidelines for treating iron deficiency in chronic kidney disease (CKD).[14]

Complications[3]

- Iron depletion may cause fatigue and reduced work performance.[6]
- Iron depletion may affect cognitive or motor development in children. However, the evidence is equivocal.
- Iron depletion may affect immune function.
- The risk of chronic lead poisoning may be increased by iron depletion.

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:[16]
    - Taking vitamin C (or foods rich in it) with meals.
    - Avoiding excess consumption of foods inhibiting iron absorption, eg tea and coffee, cows' milk.
    - For babies, breast-feeding and a suitable weaning diet.[17]

- Treatment of intestinal parasite infections.
- Routine iron supplementation or fortification of foods is feasible. However, untargeted iron supplementation may have adverse effects; its benefits and harms are debated.[3] [18]
- Screening programmes for high-risk groups have been used.

Further reading & references

- Firkin F. Interpretation of biochemical tests for iron deficiency. Australian Prescriber 1997;20:74-6
- Veggie-Diets - Protecting your Health, A guide to vegetarian and vegan diets for healthcare professionals. Vegetarian.org.uk website

1. Iron deficiency, Sydpath. The pathology service of St Vincent's Hospital, Sydney, Australia, March 2006; Useful summary of blood tests for iron status
2. Guidelines for the Management of Iron Deficiency Anaemia, British Society for Gastroenterology, May 2005
3. Zimmermann MB, Hurrell RF; Nutritional iron deficiency. Lancet. 2007 Aug 11;370(9586):511-20. [abstract]
4. Nielsen P, Nachtigall D; Iron supplementation in athletes. Current recommendations. Sports Med. 1998 Oct;26(4):207-16. [abstract]
5. Zoller H, Vogel W; Iron supplementation in athletes--first do no harm. Nutrition. 2004 Jul-Aug;20(7-8):615-9. [abstract]
6. Verdon F, Burnand B, Stubi CL, et al; Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. BMJ. 2003 May 24;326(7399):1124. [abstract]
7. Singhi S, Ravishanker R, Singhi P, et al; Low plasma zinc and iron in pica. Indian J Pediatr. 2003 Feb;70(2):139-43. [abstract]
8. Cotter PE, O'Keeffe ST; Cotter PE, O'Keeffe ST; Restless leg syndrome: is it a real problem? Ther Clin Risk Manag. 2006 Dec;2(4):465-75. [abstract]
9. Galloway MJ, Smellie WS; Investigating iron status in microcytic anaemia. BMJ. 2006 Oct 14;333(7572):791-3.
10. Nanas JN, Matsouka C, Karageorgopoulos D, et al; Etiology of anemia in patients with advanced heart failure. J Am Coll Cardiol. 2006 Dec 19;48(12):2485-9. Epub 2006 Nov 28. [abstract]
11. Suominen P, Punnonen K, Rajamaki A, et al; Serum transferrin receptor and transferrin receptor-ferritin index identify healthy subjects with subclinical iron deficits. Blood. 1998 Oct 15;92(8):2934-9. [abstract]
12. Guha K; Investigating iron status in microcytic anaemia: causes and management of iron deficient anaemia. BMJ. 2006 Nov 4;333(7575):972.
13. Iron deficiency anaemia, Map of Medicine (Haematology and haemostasis)
14. Anaemia management in chronic kidney disease, Royal College of Physicians, London, 2006; National clinical guideline
15. Anderson RP; Coeliac disease. Aust Fam Physician. 2005 Apr;34(4):239-42. [abstract]
16. Heath AM et al. Can Dietary Treatment of Non-Anemic Iron Deficiency Improve Iron Status? Journal of the American College of Nutrition, 2001
17. Griffin IJ, Abrams SA; Iron and breastfeeding. Pediatr Clin North Am. 2001 Apr;48(2):401-13. [abstract]
18. Hollan S, Johansen KS; Adequate iron stores and the 'Nil nocere' principle. Haematologia (Budap). 1993;25(2):69-84. [abstract]

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