Iron has a pivotal role in many metabolic processes, and the average adult contains 3–5 g of iron, of which two-thirds is in the oxygen-carrying molecule haemoglobin.

A normal Western diet provides about 15 mg of iron daily, of which 5–10% is absorbed (~1 mg), principally in the duodenum and upper jejunum, where the acidic conditions help the absorption of iron in the ferrous form. Absorption is helped by the presence of other reducing substances, such as hydrochloric acid and ascorbic acid. The body has the capacity to increase its iron absorption in the face of increased demand – for example, in pregnancy, lactation, growth spurts and iron deficiency (Box 1.1).

Once absorbed from the bowel, iron is transported across the mucosal cell to the blood, where it is carried by the protein transferrin to developing red cells in the bone marrow. Iron stores comprise ferritin, a labile and readily accessible source of iron, and haemosiderin, an insoluble form found predominantly in macrophages.

About 1 mg of iron a day is lost from the body in urine, faeces, sweat and cells shed from the skin and gastrointestinal tract. Menstrual losses of an additional 20 mg a month, and the increased requirements of pregnancy (500–1000 mg) contribute to the higher incidence of iron deficiency in women of reproductive age (Table 1.1, Box 1.2).

### Clinical features of iron deficiency

The symptoms accompanying iron deficiency depend on how rapidly the anaemia develops. In cases of chronic, slow blood loss, the body adapts to the increasing anaemia, and patients can often tolerate extremely low concentrations of haemoglobin (e.g. <70 g/L) with remarkably few symptoms. Most patients complain of increasing lethargy and dyspnoea. More unusual symptoms are headaches, tinnitus, taste disturbance and restless leg syndrome. Pica (a desire to eat non-food substances) and, most characteristically, pagophagia (abnormal consumption of ice) are uncommon but well described, resolving promptly with iron replacement. In children, chronic iron-deficiency anaemia can lead to impaired psychomotor and cognitive development.

On examination, several skin, nail and other epithelial changes may be seen in chronic iron deficiency. Atrophy of the skin occurs in about a third of patients, and (rarely nowadays) nail changes such as...
koilonychia (spoon-shaped nails) may result in brittle, flattened nails (Figure 1.1). Patients may also complain of angular stomatitis, in which painful cracks appear at the angle of the mouth, sometimes accompanied by glossitis. Although uncommon, oesophageal and pharyngeal webs can be a feature of iron-deficiency anaemia (consider this in middle-aged women presenting with dysphagia).

These changes are believed to be due to a reduction in the iron-containing enzymes in the epithelium and gastrointestinal tract. Few of these epithelial changes are seen in modern practice, and are of limited diagnostic value.

Tachycardia and cardiac failure may occur with severe anaemia irrespective of cause, and in such cases prompt remedial action should be taken.

When iron deficiency is confirmed, a full clinical history including leading questions on possible gastrointestinal blood loss or malabsorption (e.g. as in coeliac disease) should be obtained. Menstrual losses should be assessed, and the importance of dietary factors and regular blood donation should not be overlooked (Figure 1.2).

### Table 1.1 Daily dietary iron requirements.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1 mg</td>
</tr>
<tr>
<td>Adolescence</td>
<td>2–3 mg</td>
</tr>
<tr>
<td>Female (reproductive age)</td>
<td>2–3 mg</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>3–4 mg</td>
</tr>
<tr>
<td>Infancy</td>
<td>1 mg</td>
</tr>
<tr>
<td>Maximum bioavailability from normal diet</td>
<td>~4 mg</td>
</tr>
</tbody>
</table>

### Box 1.2 Causes of iron-deficiency anaemia.

Most iron-deficiency anaemia is the result of blood loss, especially in affluent countries.

**Reproductive system**
- Menorrhagia

**Gastrointestinal tract**

**Bleeding**
- Oesophagitis
- Oesophageal varices
- Hiatus hernia (ulcerated)
- Peptic ulcer
- Inflammatory bowel disease
- Haemorrhoids (rarely)
- Carcinoma: stomach, colorectal
- Angiodysplasia
- Hereditary haemorrhagic telangiectasia (rare)
- Hookworm infection – commonest cause of iron deficiency worldwide

**Malabsorption**
- Coeliac disease
- Atrophic gastritis (also may result from iron deficiency)
- Infection: *Helicobacter pylori*, tropical sprue
- Post-surgical: gastric bypass, small bowel resection

**Renal tract**
- Haematuria – *Schistosoma haematobium* infection
- Intravascular haemolysis with renal haemosiderin excretion

**Physiological (increased demand)**
- Growth spurts (especially in premature infants)
- Pregnancy, lactation

**Dietary**
- Vegans
- Elderly
- Infants under 12 months fed predominantly on cow’s milk

**Other**
- Iatrogenic: multiple blood sampling (especially premature infants)
- Patients with chronic renal failure undergoing haemodialysis and receiving erythropoietin

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**Figure 1.1** Nail changes in iron-deficiency anaemia (koilonychia).

**Figure 1.2** Diagnosis and investigation of iron-deficiency anaemia.
Diet alone is seldom the sole cause for iron-deficiency anaemia in adults in Britain except when it prevents an adequate response to a physiological challenge – as in pregnancy, for example. In children, by contrast, diet is a key factor, particularly in infants slow to wean (e.g. by 6 months) or those fed cow’s milk (which has low iron content and poor bioavailability) before 12 months.

**Laboratory investigations**

A full blood count and film should be assessed (Box 1.3). These will confirm the anaemia, and recognising the indices of iron deficiency is usually straightforward – reduced haemoglobin concentration, reduced mean cell volume (MCV), reduced mean cell haemoglobin (MCH), reduced mean cell haemoglobin concentration (MCHC). Some modern analysers will determine the percentage of hypochromic red cells, which may be high before the anaemia develops (it is worth noting that a reduction in haemoglobin concentration is a late feature of iron deficiency – the first change being an increase in the red cell distribution width). There may be a reactive thrombocytosis. The blood film shows microcytic hypochromic red cells, pencil cells and occasional target cells (Table 1.2, Figure 1.3).

Hypochromic anaemia occurs in other disorders, such as anaemia of chronic disorders and sideroblastic anaemias and in globin synthesis disorders, such as thalassaemia (Table 1.3). Difficulties in diagnosis arise when more than one type of anaemia is present – for example, iron deficiency and folate deficiency in malabsorption, in a population where thalassaemia is present, or in pregnancy, when the interpretation of red cell indices may be difficult. To help to
differentiate the type, further haematinic assays are used. Iron levels alone are unhelpful due to wide diurnal variation and poor sensitivity. Low levels in combination with a raised total iron binding capacity (or transferrin) – often expressed as a reduced transferrin saturation – are more suggestive.

The haematinic measure of choice is serum ferritin, reduced levels being highly specific for iron deficiency. However, its sensitivity is limited, in part because, as an acute-phase protein, the concentration may be normal or even raised in inflammatory or malignant disease. A prime example of this is found in rheumatoid disease, in which active disease may result in a spuriously raised serum ferritin concentration masking an underlying iron deficiency caused by gastrointestinal bleeding after non-steroidal analgesic treatment. There may also be confusion in liver disease, as the liver contains stores of ferritin that are released after hepatocellular damage, leading to raised serum ferritin concentrations. In cases where ferritin estimation is likely to be misleading, the soluble transferrin receptor (sTfR) assay may aid the diagnosis. Transferrin receptors are found on the surface of red cells in greater numbers in iron deficiency; a proportion of receptors are shed into the plasma and can be measured. sTfR is not increased in inflammatory disorders, and hence can help differentiate between anaemia due to inflammation from iron deficiency. Zinc protoporphyrin (ZPP) is another alternative assay. Levels rise in iron deficiency as zinc takes the place of iron in the final stage of haem synthesis. However, ZPP is elevated (albeit to a lesser degree) whenever there is impaired ability to utilise iron, which includes chronic inflammatory states and thalassaemia.

Diagnostic bone marrow sampling is seldom performed in simple iron deficiency, but if the diagnosis is in doubt a marrow aspirate may be carried out to demonstrate absent bone marrow stores.

When iron deficiency has been diagnosed, the underlying cause should be investigated and treated. Often the history will indicate the likely source of bleeding – for example, menstrual blood loss or gastrointestinal bleeding. If there is no obvious cause, further investigation generally depends on the age and sex of the patient. Coeliac serology should be sent even if the patient has no gastrointestinal symptoms, as coeliac disease may present with iron deficiency alone. In male patients and postmenopausal women, possible gastrointestinal blood loss is investigated by visualisation
of the gastrointestinal tract via endoscopy (upper and lower). It may occasionally be necessary to proceed to radiographic or wireless capsule investigation of the small bowel if endoscopies are normal and clinical suspicion remains high.

**Management**

Effective management of iron deficiency relies on (a) the appropriate management of the underlying cause (e.g. gastrointestinal or menstrual blood loss) and (b) iron replacement therapy.

Oral iron replacement therapy with gradual replenishment of iron stores and restoration of haemoglobin is the preferred treatment (Table 1.4, Figure 1.4). Oral ferrous salts are the treatment of choice (ferric salts are less well absorbed) and usually take the form of ferrous sulphate 200 mg three times daily (providing 65 mg × 3 = 195 mg elemental iron per day). Alternative preparations include ferrous gluconate and ferrous fumarate. All three compounds, however, are associated with a high incidence of side effects, including nausea, constipation and diarrhoea. These side effects may be reduced by taking the tablets after meals, but even milder symptoms account for poor compliance with oral iron supplementation. These lower gastrointestinal symptoms are not always dose related. Modified-release preparations have been developed to reduce side effects but in practice prove expensive and often release the iron beyond the sites of optimal absorption.

Effective iron replacement therapy should result in a rise in haemoglobin concentration of around 1 g/L per day (about 20 g/L every 3 weeks), with a response seen within 5–7 days, but this varies from patient to patient. Once the haemoglobin concentration is within the normal range, iron replacement should continue for 3 months to replenish the iron stores.

**Failure to respond to oral iron therapy**

The main reason for failure to respond to oral iron therapy is poor compliance. However, if the losses (e.g. bleeding) exceed the amount of iron absorbed daily, the haemoglobin concentration will not rise as expected; this will also be the case in combined deficiency states.

The presence of underlying inflammation or malignancy may also lead to a poor response to therapy. Occasionally, malabsorption of iron, such as that seen in coeliac disease, may lead to a failure to respond. High levels of dietary phytates (bran, oats, rye), polyphenols (tea) and calcium may impair absorption of iron if taken together. Finally, an incorrect diagnosis of iron-deficiency anaemia should be considered in patients who fail to respond adequately to iron replacement therapy.

**Intravenous iron preparations**

Parenteral iron may be used when the patient cannot tolerate oral supplements – for example, when patients have severe gastrointestinal side effects or if the losses exceed the daily amount that can be absorbed orally. Patients on renal dialysis receiving erythropoietin also routinely require intravenous iron.

Intravenous iron should be given under strict medical supervision (e.g. on a haematology day unit) due to the risk of anaphylaxis or other reactions. Full resuscitation facilities must be available, and a test dose is recommended before administration of the full dose. Preparations include Venofer and Ferinject, given in several divided doses, and Cosmofer and Monofer, which can be administered as a single total dose infusion (Box 1.4).

The dose is based on the estimated iron deficit, calculated using the Ganzoni formula (Box 1.5). In practice, quick reference tables are available giving the dose for the patient’s weight and target versus actual haemoglobin level.

### Table 1.3 Characteristics of anaemia associated with other disorders.

<table>
<thead>
<tr>
<th></th>
<th>Iron deficiency</th>
<th>Chronic disorders</th>
<th>Thalassaemia trait (α or β)</th>
<th>Sideroblastic anaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Degree of anaemia</td>
<td>Any</td>
<td>Seldom &lt;90 g/L</td>
<td>Mild</td>
<td>Any</td>
</tr>
<tr>
<td>MCV</td>
<td>↓</td>
<td>N or ↓</td>
<td>↓</td>
<td>N or ↓ or ↑</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>↓</td>
<td>N or ↑</td>
<td>N</td>
<td>↑</td>
</tr>
<tr>
<td>Soluble transferrin receptor assay</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zinc protoporphyrin</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑ or ↑↑</td>
</tr>
<tr>
<td>Marrow iron</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
</tbody>
</table>

N: normal.

### Table 1.4 Elemental iron content of various oral iron preparations.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Amount (mg)</th>
<th>Ferrous iron (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous sulphate</td>
<td>200</td>
<td>65</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300</td>
<td>35</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>210</td>
<td>65–70</td>
</tr>
</tbody>
</table>

Figure 1.4 Oral iron replacement therapy.
The rise in haemoglobin concentration is no faster with parenteral iron preparations than with oral iron therapy.

**Alternative treatments**

Blood transfusion is not indicated unless the patient has decompensated due to a drop in haemoglobin concentration and needs a more rapid rise in haemoglobin – for example, in cases of worsening angina or severe coexisting pulmonary disease. In cases of iron deficiency with serious ongoing acute bleeding, blood transfusion may be required.

**Prevention**

When absorption from the diet is likely to be matched or exceeded by losses, extra sources of iron should be considered – for example, prophylactic iron supplements in pregnancy, for premature infants or after gastrectomy, or encouragement of breast feeding or use of formula milk rather than cow’s milk during the first year of life.

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**Further reading**


