Iron deficiency: still under-diagnosed?

Anaemia resulting from iron deficiency is one of the commonest diseases affecting humankind. Although its diagnosis and management may be straightforward, iron deficiency is underdiagnosed in nations with structured health-care systems, mainly because of a lack of awareness of its existence in selected clinical scenarios.

Iron deficiency is the most widespread nutritional disorder in the world. It not only affects individuals in poorly-resourced countries, but is also significantly prevalent in developed nations. The common causes of iron deficiency are shown in *Table 1*. Iron is one of the most physiologically relevant metals in the human body. It plays an important role in the functioning of various organs and organ systems by being the predominant oxygen-carrying protein and a key component of the enzymes involved in metabolic and oxidative reactions (*Figure 1*).

Huge advances have occurred in the understanding of iron homeostasis with the discovery of the molecule, hepcidin, a key regulator of iron absorption. The role of hepcidin in iron metabolism is summarized in *Figure 2*. Serum ferritin is the most specific biochemical test which is helpful in diagnosing iron deficiency. However, as shown in *Figure 2*, ferritin is an iron storage protein and in inflammatory states, when the hepcidin levels are high, serum ferritin levels can be 'falsely high' even though the amount of circulating iron is low. This reduces the value of serum ferritin measurement in diagnosing iron deficiency in the presence of a coexisting inflammatory process.

Table 1. Causes of iron deficiency anaemia

Blood loss — commonest cause	When not obvious, commonest cause is gastrointestinal bleeding
	Iatrogenic anaemia through frequent blood tests is overlooked
Decreased iron intake – malnutrition or poor nutrition	
Decreased iron absorption	Achlorhydria and antacids
	Atrophic gastritis
	Helicobacter pylori infection
	Coeliac disease
	Gastric bypass surgery
	Food interference – phytates in oats and bran, large amounts of tea or calcium
Rare causes	Haemoglobinuria in relation to intravascular haemolysis
	Loss of iron into the lungs in pulmonary haemosiderosis
	Congenital iron deficiency caused by genetic mutations including iron-refractory iron deficiency anaemia

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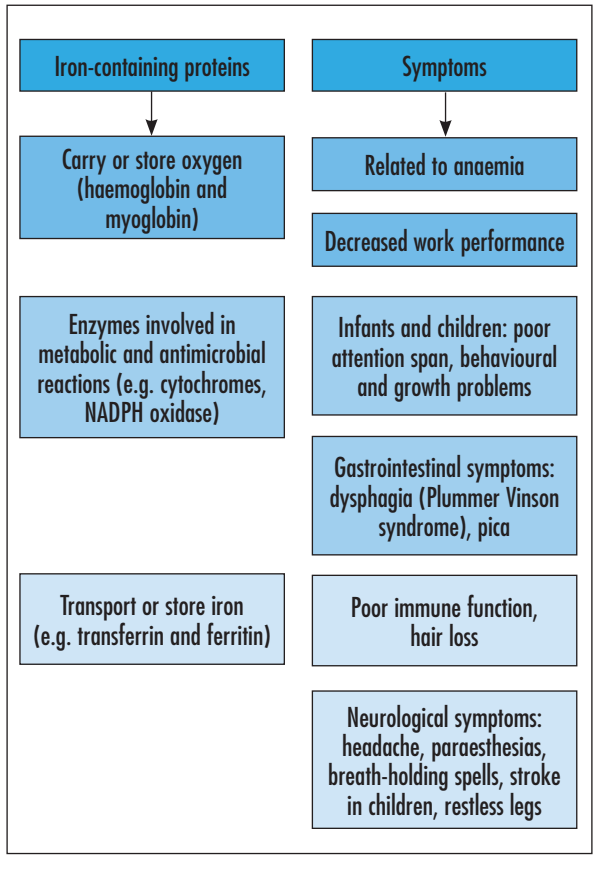
Iron deficiency and fatigue

Fatigue is one of the commonest symptoms for which individuals attend the GP. Iron deficiency anaemia is often considered in the differential diagnosis of fatigue but excluded once a normal haemoglobin level is noted. The possibility of iron deficiency without anaemia is not considered in such cases, although when present and treated this can have a significant impact as shown by Vaucher and colleagues (2012). They recruited nearly 200 women of reproductive age who complained of fatigue and had a ferritin level less than 50 ug/litre but haemo-

Figure 1. Iron proteins and symptoms of iron deficiency. NADPH = nicotinamide adenine dinucleotide phosphate.



globin greater than 120 g/litre to receive either oral iron or placebo for 12 weeks. Iron supplementation decreased fatigue (assessed by the Current and Past Psychological Scale) by almost 50% from baseline, and also improved haemoglobin and ferritin levels, suggesting the importance of this treatment even in the absence of anaemia. Similar results were shown almost a decade earlier in non-anaemic women with unexplained fatigue and similar serum ferritin concentrations (Verdon et al, 2003).

More recently, a randomized, double-blinded, placebo-controlled study demonstrated the efficacy of intravenous iron in treating fatigue in non-anaemic women (haemoglobin ≥120 g/litre) with serum ferritin concentration ≤50 ug/litre. Fatigue index decreased by 1.8 in the iron group compared with 0.4 in the placebo group (P=0.005), and improved by 82% of iron-treated compared with 47% of placebo-treated patients (P=0.03)(Krayenbühl et al, 2011). Despite these results, it is still considered acceptable for women to have lower haemoglobin values when a short course of iron treatment may cure their fatigue and related symptoms. Although similar work has not been done in men or older persons, the same scenario has been explored in endurance athletes, where a meta-analysis found that iron treatment had a moderate to large effect on improving laboratory iron markers and a moderate effect on improving aerobic capacity (Burden et al, 2014).

In summary, it is important to be aware that iron deficiency can exist in the absence of a decrease in haemoglobin level and can cause varied symptoms. This may be related to the fact that the iron requirements differ for different individuals and a serum ferritin level in the normal range may not always exclude iron deficiency. A short course of iron in such cases is unlikely to be harmful but may prove beneficial. However, several questions remain which will hopefully be addressed in future trials:

- How much iron should be given?
- Is intravenous iron safe in this setting?
- Can a specific marker other than fatigue be used as a marker for the replacement therapy?
- Can we have a more accurate ferritin cut-off (von Drygalski and Adamson, 2011)?

Iron deficiency of cardiac failure

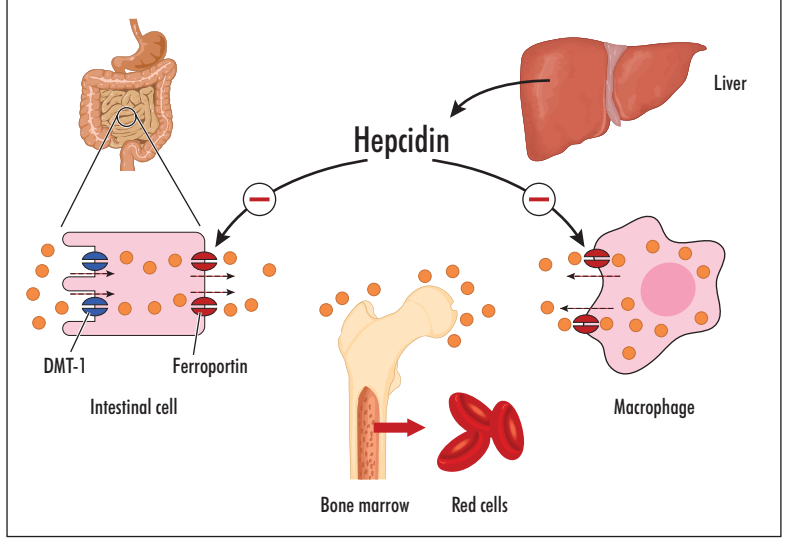
Iron deficiency is also a significant but overlooked problem in patients who develop congestive cardiac failure, one of the commonest reasons for hospital admissions. A meta-analysis of patients with congestive cardiac failure showed 37% of 153 180 patients were anaemic and this was associated with an increased mortality risk (odds ratio 1.96) in patients with either systolic or diastolic congestive cardiac failure (Groenveld et al, 2008). Although the aetiology of anaemia in these cases is multifactorial, iron deficiency is a common and modifiable cause. In a prospective observational study, where iron deficiency was defined as ferritin <100 µg/litre, or 100–300 µg/litre with transferrin saturation <20%, the prevalence of iron deficiency was 37% and was related to an increased risk of death or need for heart transplant (Jankowska et al, 2010). To confirm the importance of iron replacement in congestive cardiac failure, the FAIR-HF trial investigators enrolled 459 patients with chronic heart failure and iron deficiency. Those who received intravenous ferric carboxymaltose rather than placebo noted significant improvements in the 6-minute walk test and quality-of-life assessments with an acceptable side-effect profile (Anker et al, 2009).

In summary, patients with congestive cardiac failure should have their serum ferritin level checked regularly even in the absence of anaemia and if the level is lower than 300 µg/litre, intravenous iron should be considered to improve their symptoms and hopefully reduce hospital admission times. A review on this topic has been published in this journal by Eyre and Littlewood (2013).

Iron deficiency of chronic obstructive pulmonary disease?

Anaemia is common in patients who have chronic obstructive pulmonary disease but once again is overlooked. Since polycythaemia or an elevated haematocrit is a physiological response to the chronic hypoxia in these patients, a normal haemoglobin value should be considered inappropriately low for patients with chronic obstructive pulmonary disease. Chambellan et al (2005) first noted the importance of anaemia for the prognosti-

Figure 2. Iron homeostasis and the role of hepcidin. Dietary iron is absorbed from gut lumen across the intestinal epithelium through a divalent metal ion transporter-1 (DMT-1) channel. Once inside, it is transported across the basolateral part of these cells through a transmembrane channel, ferroportin. This latter process is controlled by hepcidin, a hormone released from the liver. The binding of hepcidin to ferroportin induces the endocytosis and proteolysis of ferroportin thus limiting the release of iron into the plasma. A similar mechanism occurs in the storage compartments of iron especially macrophages where hepcidin regulates release of iron through ferroportin. The production of hepcidin is regulated by body content of iron; more hepcidin is produced when iron is abundant which then limits further iron absorption and release from stores and vice versa. During erythropoiesis, hepcidin is inhibited so that iron is channelled to bone marrow to allow red cell production. In inflammatory states, hepcidin is increased which causes decreased levels of iron in the circulation leading to anaemia of chronic disease.



cation of patients with chronic obstructive pulmonary disease who were on long-term oxygen therapy. Multivariate analysis from this work found the haematocrit to be an independent predictor of survival, hospital admission rate and duration of hospitalization. The difference in 3-year survival was also striking, being 24% when the haematocrit was <35% compared to 70% when the haematocrit was >55%. A large retrospective cohort study from the USA identified 33% of the 2404 patients with chronic obstructive pulmonary disease with a diagnosis of anaemia with annual costs being more than twice those for patients without anaemia (Shorr et al, 2008). Health resource utilization was also significantly greater in these patients and was independent of demographic and clinical patient characteristics.

Although anaemia is common in patients with chronic obstructive pulmonary disease, its aetiology has not been characterized. Since chronic obstructive pulmonary disease is an inflammatory disease, it is logical to assume that the anaemia is that of chronic disease. However, as discussed later in this article (see sections on anaemia in patients with congestive cardiac failure and renal impairment), functional iron deficiency can contribute to anaemia in patients with chronic obstructive pulmonary disease as well. It is possible that if a higher target ferritin level and additional laboratory parameters like transferrin saturation are used, intravenous iron replacement may prove to be beneficial in chronic obstructive pulmonary disease patients as well and may decrease exacerbations and hospitalizations and improve their quality of life. This concept was examined by a small study which needs confirmation in bigger trials. Silverberg et al (2014) examined the investigations and treatment profile of all patients with an acute exacerbation of chronic obstructive pulmonary disease. They found that 47 out of 107 consecutive patients hospitalized with chronic obstructive pulmonary disease were anaemic on admission. Of the 47 anaemic patients 18 had undergone investigations for iron deficiency; all had iron deficiency but none were treated with iron. Eleven out of 12 outpatients with chronic obstructive pulmonary disease and anaemia also had iron deficiency based on lab parameters, suggesting that lack of iron is common in chronic obstructive pulmonary disease patients but is overlooked and undertreated.

Table 2. Causes of poor response to oral iron replacement in older individuals

Poor compliance as a result of gastrointestinal side effects
Continuing blood loss
Undiagnosed coeliac disease
Alterations in gastric acidity which affects iron absorption
Concomitant *Helicobacter pylori* infection
Copious tea drinking and concurrent medications such as calcium can affect iron absorption
High phytate intake (e.g. cereals)
Alternatives to ferrous sulphate have less elemental iron and may not be as effective

Iron deficiency in perioperative patients

Anaemia is predictive of poor outcomes in surgical patients, and it is not just moderate to severe decreases in haemoglobin which lead to increased morbidity and mortality. In patients undergoing major non-cardiac surgery, even mild anaemia (haematocrit concentration >29–<39% in men and >29–<36% in women) was independently associated with an increased risk of 30-day morbidity and mortality (Musallam et al, 2011). It is necessary to investigate the cause of anaemia in all these cases, although surgical units may overlook the importance and fail to pursue the aetiology of mild anaemia.

If the haemoglobin level is optimized in all patients, including those with mild anaemia, it may be possible to reduce transfusions in the postoperative stage especially since blood transfusions are increasingly recognized as predictors of poor outcome and as leading to an increased risk of postoperative infections in surgical patients (Rohde et al, 2014). So, what is the alternative in these patients? Also, how can we 'prevent' the need for postoperative transfusions by pre-empting blood loss? Both these are answered by the good practice point proposed by the multidisciplinary panel convened by Network for Advancement of Transfusion Alternatives (Beris et al, 2008). This states that: 'Non-anaemic patients with a serum ferritin level <100 ng/ml or ferritin 100–300 ng/ml and transferrin saturation <20% undergoing surgical procedures with an expected blood loss >1500 ml (haemoglobin drop of 30–50 g/litre) may benefit from preoperative oral or i.v. [intravenous] iron administration, depending on the presence of co-morbidities and on the timescale before surgery.'

Iron deficiency in older people

One of the commonest causes of anaemia in older people is iron deficiency. In a study of over 250 subjects aged 65 years or over, anaemia was found in 25.4% while low serum ferritin levels were observed in 16.8% of men and 6% of women (Lopez-Contreras et al, 2010). This problem of iron deficiency is often well recognized but the deficiency is often not fully treated. Most of these patients get oral iron which is often 'not effective' for various reasons (*Table 2*). Dietary iron absorption is dependent on gastric acid which reduces it into the ferrous state to facilitate the absorptive process.

Reduced gastric acidity or hypochlorhydria is common in older people for various reasons including atrophic gastritis and the intake of proton pump inhibitors (Hershko and Camaschella, 2014). Atrophic gastritis is a common cause of iron deficiency in patients who do not have gastrointestinal symptoms or other potential causes of gastrointestinal bleeding (Annibale et al, 2001). In one study, patients with a long history of iron deficiency anaemia and *Helicobacter pylori*-associated gastritis had

eradication therapy with two antibiotics and discontinuation of iron replacement therapy (Annibale et al, 1999). At 6 months, 75% of patients had recovered from anaemia while after 12 months, 91.7% of patients had recovered from anaemia, demonstrating the importance of this management strategy. A meta-analysis from Asia, where there is a higher incidence of both iron deficiency and *H. pylori*, showed eradication therapy for *H. pylori* combined with iron administration is more effective than iron administration alone for the treatment of iron deficiency anaemia (Huang et al, 2010).

Undiagnosed coeliac disease is another often overlooked cause of iron deficiency in the elderly (Rashtak and Murray, 2009). A survey of 2440 coeliac patients in the USA reported that 16% of patients were over the age of 65 years when they were diagnosed with coeliac disease, similar to the percentage of patients diagnosed before 18 years of age (Patel et al, 2005). Thus if a diagnosis of coeliac disease is not made, iron deficiency related to it will be overlooked.

From a laboratory point of view, diagnosis of iron deficiency in the elderly is not straightforward since many have concomitant chronic diseases which can elevate the ferritin level and thus 'mask' iron deficiency. Traditional tests like mean corpuscular volume are often normal in older patients with iron deficiency as a result of concomitant folate or vitamin B_{12} deficiency, or myelodysplasia. More recent publications suggest that a higher mean corpuscular volume observed in selected older people may be an indicator of prognosis in acute decompensated heart failure (Ueda et al, 2013).

Probably the biggest issue in the context of anaemia in elderly patients is the failure to recognize that a haemoglobin level lower than normal is not acceptable for older people and that mild anaemia can have clinical implications by affecting cardiac and cerebrovascular functions and musculoskeletal health (Merchant and Roy, 2012).

Iron deficiency in renal patients

Since haemoglobin concentration starts to decrease when the estimated glomerular filtration rate reduces, most patients with chronic kidney disease suffer from anaemia. Anaemia is also a significant contributor to a reduced quality of life in these patients and adds a great deal to the morbidity of these patients (Locatelli et al, 2004). Although anaemia in chronic kidney disease can be multifactorial, one of the main causes is iron deficiency. There are several reasons for the development of iron deficiency in patients with chronic kidney disease including poor appetite, altered diet (required because of the need to reduce protein intake), regular venesections and blood loss from haemodialysis and abnormal gastrointestinal bleeding which may occur with uraemic platelet dysfunction (Macdougall and Geisser, 2013). There is also the additional issue of 'functional' iron deficiency which is defined as a 'state in which there is insufficient iron in erythroid precursors despite apparently adequate body iron stores, confirmed by the presence of stainable iron in the bone marrow together with a normal serum ferritin value' (Thomas et al, 2013).

Chronic kidney disease is probably the commonest cause of functional iron deficiency anaemia and is recognized by the renal physicians as an important concern. This has been addressed in the KDIGO clinical practice guideline for anaemia in chronic kidney disease (National Kidney Foundation, 1997; Kidney Disease: Improving Global Outcomes (KDIGO) Anaemia Working Group, 2012). It recommends prescription of iron in patients with anaemia after balancing the potential benefits of avoiding or minimizing blood transfusions, erythropoietin use, and anaemia-related symptoms against the harm caused by allergic reactions. They give a grade 2C recommendation for a trial of intravenous iron for adult patients with chronic kidney disease and anaemia who are not on iron or erythropoietin therapy and also for adult patients with chronic kidney disease who are on erythropoietin therapy and are not receiving iron supplementation. They advise an increase in haemoglobin concentration and ferritin 500 ug/litre as targets for intravenous iron therapy (Kidney Disease: Improving Global Outcomes (KDIGO) Anaemia Working Group, 2012).

Iron deficiency in pregnancy

Anaemia is the most common haematological complication during pregnancy. Although physiological anaemia of pregnancy is common in pregnancy as a result of the dilutional effect of the increased plasma volume, haemoglobin values less than 110 g/litre should lead to consideration of iron deficiency as a cause for the lower values. Although a link between severe anaemia and poor pregnancy outcome has been reported, a recent Cochrane database review found no substantial evidence to confirm this association (Brabin et al, 2001; Peña-Rosas et al, 2015). Maternal iron deficiency has also been correlated with problems with motor and intellectual development in infants and suggested to affect their emotional behaviour (Pavord et al, 2012).

Since there is variation in what is considered as normal haemoglobin levels in pregnancy, the British Committee for Standards in Haematology guidelines recommend a level less than 110 g/litre in the first trimester, less than 105 g/litre in the second and third trimesters and less than 100 g/litre in the postpartum period as indicative of anaemia (Milman et al, 2007; Pavord et al, 2012). Owing to the huge impact iron has on the wellbeing of pregnant women, the British Committee for Standards in Haematology guidelines recommend a trial of iron in all pregnant women with anaemia once haemoglobinopathy is ruled out (Pavord et al, 2012). The threshold recommended for serum ferritin is 15 µg/litre for diagnosing definite iron deficiency and below 30 µg/litre for possible iron deficiency (Pavord et al, 2012). Since gastrointestinal side effects are more common in pregnancy and can also be associated with iron therapy, preparations with lower

iron content should be tried. On treatment, the haemoglobin level should be monitored and once in the normal range, further treatment should be given for another 3 months and at least 6 weeks postpartum to boost iron stores. A grade 1A recommendation has been given for parenteral iron in those who do not respond to oral iron from the second trimester (Pavord et al, 2012). Although universal supplementation of iron may be appropriate in certain poorly resourced areas this may not have the same benefit in developed nations and is not recommended.

Conclusions

Iron deficiency can have significant clinical implications even in the absence of anaemia. Physicians should be able to recognize iron deficiency in various clinical scenarios and treat them appropriately as this can lead to significant clinical, psychological, financial and social benefits. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Iron deficiency as a cause of morbidity in patients from the well-resourced nations is often overlooked.
- Functional iron deficiency is under-recognized in certain clinical scenarios like congestive cardiac failure and chronic obstructive pulmonary disease.
- It is not acceptable for women and older people to have lower than normal haemoglobin range.