Scandinavian Journal of Clinical and Laboratory Investigation

ISSN: 0036-5513 (Print) 1502-7686 (Online) Journal homepage: http://www.tandfonline.com/loi/iclb20

Iron deficiency and iron deficiency anemia in women

Jane Coad & Kevin Pedley

To cite this article: Jane Coad & Kevin Pedley (2014) Iron deficiency and iron deficiency anemia in women, Scandinavian Journal of Clinical and Laboratory Investigation, 74:sup244, 82-89, DOI: 10.3109/00365513.2014.936694

To link to this article: https://doi.org/10.3109/00365513.2014.936694

Scandinavian Journal of Clinical & Laboratory Investigation, 2014; 74(Suppl 244): 82–89

informa
healthcare

ORIGINAL ARTICLE

Iron deficiency and iron deficiency anemia in women

JANE COAD & KEVIN PEDLEY

Institute of Food, Nutrition & Human Health, College of Health Te Kura Hauora Tangata, Massey University, Palmerston North, New Zealand

Abstract

Iron deficiency is one of the most common nutritional problems in the world and disproportionately affects women and children. Stages of iron deficiency can be characterized as mild deficiency where iron stores become depleted, marginal deficiency where the production of many iron-dependent proteins is compromised but hemoglobin levels are normal and iron deficiency anemia where synthesis of hemoglobin is decreased and oxygen transport to the tissues is reduced. Iron deficiency anemia is usually assessed by measuring hemoglobin levels but this approach lacks both specificity and sensitivity. Failure to identify and treat earlier stages of iron deficiency is concerning given the neurocognitive implications of iron deficiency without anemia. Most of the daily iron requirement is derived from recycling of senescent erythrocytes by macrophages; only 5–10 % comes from the diet. Iron absorption is affected by inhibitors and enhancers of iron absorption and by the physiological state. Inflammatory conditions, including obesity, can result in iron being retained in the enterocytes and macrophages causing hypoferremia as a strategic defense mechanism to restrict iron availability to pathogens. Premenopausal women usually have low iron status because of iron loss in menstrual blood. Conditions which further increase iron loss, compromise absorption or increase demand, such as frequent blood donation, gastrointestinal lesions, athletic activity and pregnancy, can exceed the capacity of the gastrointestinal tract to upregulate iron absorption. Women of reproductive age are at particularly high risk of iron deficiency and its consequences however there is a controversial argument that evolutionary pressures have resulted in an iron deficient phenotype which protects against infection.

Key Words: *Absorption, blood donation, cognitive function, hepcidin, iron deficiency without anemia, nutrition, obesity*

Introduction

Despite iron being one of the most abundant elements in the earth's crust, iron deficiency is the most common nutritional problem worldwide and presents significant public health challenges. Iron deficiency (ID) and iron deficiency anemia (IDA) disproportionately affect women and children. WHO estimates that over 2.10^9 people, about a third of the population of the world, are anemic, predominantly due to iron deficiency.

Premenopausal women are vulnerable to ID partly because of iron lost in menstrual blood but also because they often have a low dietary iron intake and may follow restrictive dietary practices to lose weight. Dietary iron recommendations are 18 mg/d for women of reproductive age compared to 8 mg/d for men [1]. Pregnancy increases iron requirements; the recommended dietary intake rises to 27 mg/d. Although iron is essential, it is also toxic; there is a delicate balance between obtaining enough iron from the diet to sustain life, via inefficient absorption mechanisms, and ensuring that excess iron is not available to generate reactive oxygen species which damage macromolecules or to support the growth of pathogens. The acquisition and transport of iron by the body reflects the evolutionary mechanisms that protect the body from free iron while promoting highly efficient mechanisms for recycling and conservation of iron. Most iron in the body (Figure 1), about 3 g in women, is present in hemoproteins and iron-containing enzymes involved in cellular respiration. Iron is also present in the plasma bound to transferrin, stored in intracellular ferritin depots and as a component of cytochromes and catalase.

Correspondence: Jane Coad, Institute of Food, Nutrition & Human Health, College of Health Te Kura Hauora Tangata, Massey University, Private Bag 11-222, Palmerston North, New Zealand 4442. E-mail: j.coad@massey.ac.nz

(Received 3 May 2014; accepted 31 May 2014)

ISSN 0036-5513 print/ISSN 1502-7686 online
DOI: 10.3109/00365513.2014.936694

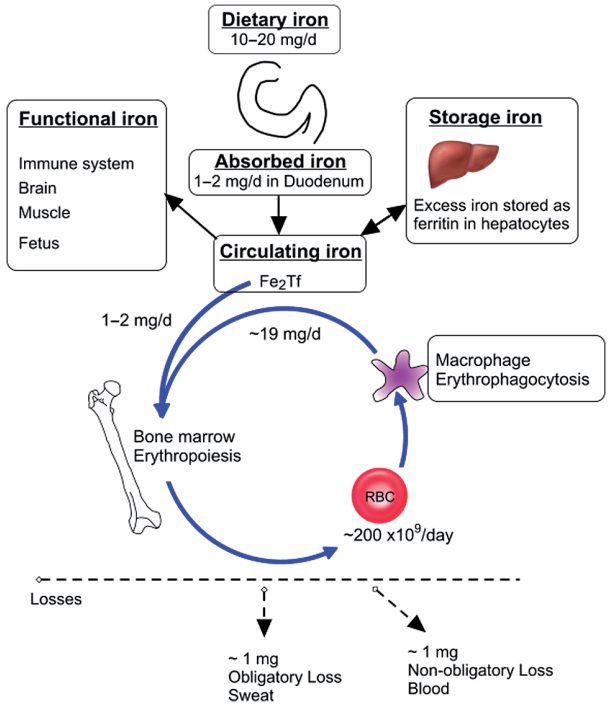


Figure 1. Iron balance in the body. Only 1–2 mg of iron is absorbed from the iron consumed in meals. Iron is required for erythropoiesis, the immune system, brain requirements and for transfer across the placenta in pregnancy. Iron in excess of requirements may be stored in the bone marrow and liver. Iron required for erythropoiesis comes predominantly from the breakdown of red blood cells (RBC) by macrophages; however about 5 % of iron required for RBC formation comes from the newly absorbed iron. The variable component of iron status is that lost in blood such as menstrual loss, blood donation, nose bleeds and gastrointestinal bleeding.

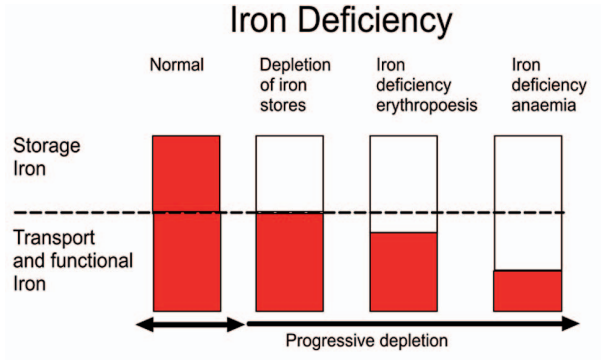
A proportion of iron is held within macrophages, the spleen and liver and in the bone marrow. Excess iron is stored in ferritin in hepatocytes.

Stages of iron deficiency

Iron deficiency can be characterized as three distinct stages (Figure 2):

- in mild deficiency, there is normal production of iron-dependent proteins;
- in marginal iron deficiency (ID), production of these proteins is compromised but hemoglobin synthesis and erythropoiesis are maintained;
- in iron deficiency anaemia (IDA) the production of hemoglobin is compromised and erythrocytes are characteristically misshapen, small (microcytic) and pale (hypochromic) with reduced hemoglobin concentrations.

In IDA, clinical symptoms become evident, including pallor and fatigue, reflecting diminished delivery of oxygen to tissues. Symptoms are less marked where ID has developed over a longer time because physiological adaption, particularly cardiovascular and respiratory, is more effective.



Iron status	Normal	Mild deficiency	Marginal deficiency	Severe deficiency
Haemoglobin	Normal	Normal	Normal	Low
Other Fe functions	Normal	Normal/low	Low	Low
Stores (SF)	Normal	Normal/low	Low	Low

Figure 2. (1) Normal with good iron stores; (2) mild deficiency where the mobilizable iron stores in the bone marrow become depleted but there is normal production of iron-dependent proteins; (3) marginal deficiency or iron deficient erythropoiesis which affects iron-dependent protein production but hemoglobin production and erythropoiesis are preserved; and (4) iron deficiency anemia (IDA) where the production of hemoglobin is compromised and red blood cell synthesis abrogated because there is insufficient iron for incorporation into erythroid precursors.

Absorption, utilization and storage of iron

Iron requirements are predominantly met by replenishment from the reticuloendothelial macrophages which acquire iron from erythrophagocytosis with a small proportion of iron (about 5 % of daily requirement or 1–2 mg per day) absorbed from the diet, predominantly by duodenal enterocytes, to replace obligatory passive losses. About 5–15 % of dietary iron is absorbed.

Dietary iron is absorbed across the gut wall (Figure 3) as both heme and non-heme iron. Heme

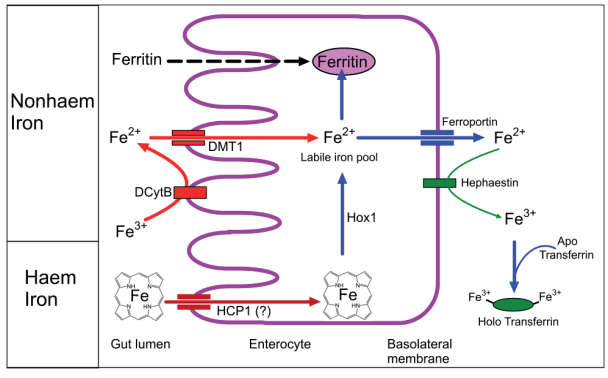


Figure 3. Dietary iron is absorbed across the gut wall as heme iron (from animal food sources) and non-heme iron (from animal and plant food sources). Furthermore, ferritin proteins may be absorbed intact, contributing to the acquisition of non-heme iron. (DMT1 – Divalent metal transporter 1; DCytB – Duodenal cytochrome B; Hox1 – heme oxygenase-1; HCP1 – Heme carrier protein 1).

is highly bioavailable compared to non-heme iron; its absorption is more efficient whereas the bioavailability of non-heme iron is affected significantly by other dietary components. Non-heme iron exists predominantly in the environment and the diet as the insoluble ferric (Fe^{3+}) form of iron but is transported across the gut wall in the ferrous (Fe^{2+}) form. Ferric iron is reduced to ferrous iron by duodenal ferrireductases such as the membrane-bound duodenal cytochrome B (DcytB) [2]. In addition, reducing agents in the diet such as ascorbic acid, lactic acid, citric acid and other organic acids, or foods which stimulate endogenous gastric acid production, also reduce Fe^{3+} to Fe^{2+} and promote iron absorption.

Transport of Fe^{2+} from the lumen of the duodenum is via the divalent metal transporter (DMT-1) which co-transports protons. DMT-1 is not specific for iron so other divalent metal ions competitively inhibit iron absorption. Within the duodenal enterocyte, iron from heme and non-heme sources enters a common pool of labile iron. Absorbed iron is then either stored intracellularly as ferritin or transported across the basolateral membrane of the enterocyte. Ferritin, a soluble 24-subunit protein complex, can sequester up to 4500 atoms of iron per molecule as ferrihydrite [3] thus restricting the availability of intracellular free iron. Iron is stored in ferritin in all cells but found at particularly high concentrations in the bone marrow and hepatic reticuloendothelial cells. This sequestration of iron in ferritin means that the duodenal enterocytes act as a short-term store of iron, buffering iron absorption in excess of requirement, during their 3–5 day migration and differentiation from stem cells at the base of the intestinal crypt until they are sloughed off from the villus tip into the gut lumen. Small quantities of ferritin subunits (without iron) are present in the serum so can indicate iron stores and iron status before hemoglobin concentration falls.

Export across the basolateral membrane of the enterocyte utilizes the iron-export protein, ferroportin [4]. Ferroportin is highly expressed by other cells that export significant amounts of iron such as the macrophages which recycle components of senescent erythrocytes. Fe^{2+} transported out of the enterocyte is immediately oxidized to Fe^{3+} by membrane-bound ferroxidases, such as hephaestin and ceruloplasmin, and then bound to transferrin (Tf). Each molecule of apo-transferrin (iron-free Tf) can bind to 2 atoms of ferric iron which are transported in the circulation to cells expressing transferrin receptors (TfR1). Tf has a high binding affinity for iron and is 25–30 % saturated under physiological conditions in healthy humans so there is negligible non-transferrin-bound iron in the plasma.

Cells which have high iron requirements, such as the immature erythroid cells in the bone marrow, or those that are rapidly dividing, such as the cells in the intestinal crypts, express very high levels of TfR1. Holo-Tf (transferrin with iron) docks to the TfR1 on the membrane of target cells. The receptor-ligand complex is endocytosed and a proton pump causes acidification of the endocytotic vesicle; the lower pH reduces the affinity of Tf for iron so iron dissociates and is released into the cytosol. Tf and TfR1 are recycled to the membrane of the cell. Fragments are cleaved from TfR so the serum concentration of soluble TfR (sTfR) reflects the demand for iron.

Iron homeostasis at the cellular level is maintained by the regulation of uptake and efflux of iron across the plasma membrane and by its storage within the cell. Key proteins involved in these processes contain Iron Response Elements (IREs) within the non-translated regions of their mRNA. Iron Regulatory Proteins (IRPs) bind to IREs to regulate the translation of mRNA into proteins and thereby maintain cellular iron homeostasis. When intracellular iron is low, IRPs bind to the IREs in TfR1 mRNA and DMT-1 mRNA and stabilize these mRNAs to increase iron uptake and maintain adequate levels. Conversely, excess intracellular iron prevents the binding of IRPs to IREs, increasing the translation of ferritin and ferroportin from mRNA reducing the threat of iron toxicity.

There is no route of excretion of excess iron; iron balance is regulated solely by iron absorption. Hepcidin, a ubiquitous cysteine-rich antimicrobial peptide produced by the liver, is the primary regulator [5]. Hepatocytes produce more hepcidin as part of the innate immune response and when iron status is adequate. Hepcidin binds to ferroportin on the enterocytes, macrophages and hepatocytes causing its internalization into endosomes and subsequent degradation thus resulting in increased intracellular sequestration of iron and inhibition of iron release into the circulation (Figure 4). The accumulation of intracellular iron inhibits the expression of DcytB and DMT-1 on the luminal surface of the enterocytes so absorption of dietary iron is decreased.

Like their human hosts, almost all human pathogens have an absolute requirement for iron. A key component of innate immune protection is to restrict availability of iron to invading pathogens; this process is termed 'nutritional immunity' [6]. Availability of iron for microbes is already low since most iron in humans is intracellular and the small amount of extracellular iron is bound with high affinity to transferrin.

Inflammatory markers such as cytokines are prominent inducers of hepcidin synthesis [7] from the liver and macrophages and neutrophils. Iron sequestration in intracellular ferritin leads to hypoferremia and decreased availability of iron for pathogens. It is this pathway that is responsible for anemia in conditions such as infection and inflammatory conditions; this anemia is refractory to oral iron therapy because the raised hepcidin levels result in iron being trapped in the enterocyte and not being

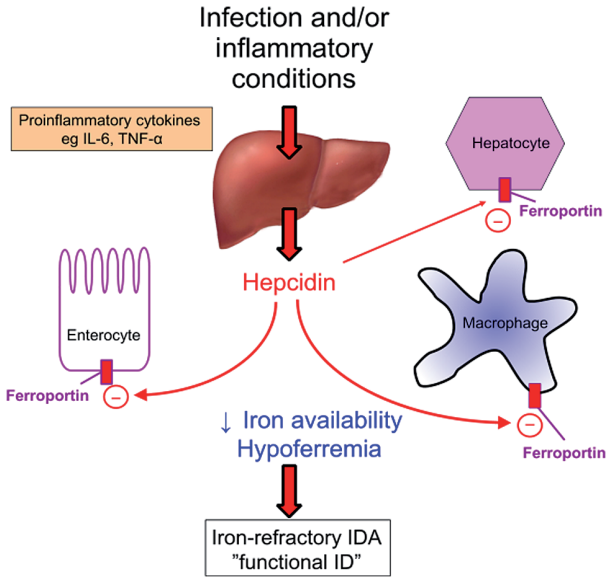


Figure 4. The principal regulator of iron status is hepcidin. Infection and inflammatory conditions increase hepatic hepcidin production via proinflammatory cytokines. Hepcidin binds to ferroportin on enterocytes, macrophages and hepatocytes resulting in its internalization and sequestration of iron in intracellular stores. This decreases iron availability for pathogens but also compromises iron availability for erythropoiesis which can cause functional anemia which is refractory to oral iron therapy.

exported into the blood. In addition the iron-binding glycoprotein lactoferrin, present in mucosal secretions, also restricts the availability of iron to potential pathogens. When bacterial pathogens enter the host they experience iron deprivation which acts as a stimulus to trigger the gene expression in the pathogen that will result in iron acquisition [6]. Bacteria have evolved a number of strategies to circumvent iron restriction by the host. These mechanisms vary in different species and include the use of non-heme or heme/hemoprotein transporters which allow uptake of non-heme or heme iron from host body fluids and many pathogens secrete siderophores which bind ferric iron with extremely high affinity and transport iron into the cell. Pathogenic bacteria that adopt an intracellular lifestyle often target host macrophages, the sites of erythrocyte degradation, which are therefore rich in iron. Many bacterial species have evolved the ability to evade phagocytic degradation, providing the ideal intracellular environment for obligate iron requiring microbes such as *Mycobacterium tuberculosis*. Restriction of iron availability to pathogens is clearly an important aspect of host defense. The importance of this is evident in iron overload syndromes, where in addition to increased cellular damage from reactive oxygen species, there is also an increased risk of infection.

Erythropoiesis is stimulated by the hormone erythropoietin produced by the kidney. It takes about 7 days for erythropoiesis to culminate in the release of reticulocytes from the bone marrow. These immature red blood cells mature in the circulation for about 24 hours during which time they acquire morphological characteristics of red blood cells, becoming smaller and losing the remnants of their nuclei. Reticulocytes usually make up about 1 % of the red blood cell mass but ID results in the increased production of larger paler reticulocytes so the proportion, color and size of reticulocytes is an indicator of ID. In the formation of hemoglobin, ferrous protoporphyrin (heme) combines with globin. In ID, zinc is substituted for iron in the final stages of erythropoiesis [8] so levels of zinc protoporphyrin in erythrocytes can also be used diagnostically.

Roles of iron

As a transition metal, iron oscillates between two stable oxidation states, the divalent ferrous (Fe^{2+}) and trivalent ferric (Fe^{3+}) species; it can donate and accept electrons readily and so participates in complex biological redox reactions. Iron is required for the functioning of hemoproteins, such as hemoglobin, involved in oxygen transport and binding, cytochromes, the mitochondrial electron transport chain and cellular metabolism, and with catalases and peroxidases, which are involved in redox reactions. Metalloproteins containing iron are essential for DNA synthesis, gene regulation, cell proliferation and differentiation, drug metabolism, synthesis of steroid hormones and the neutrophil respiratory burst of phagocytosis.

There is a hierarchy of iron use in the body; erythropoiesis is protected when there is not enough iron available for all biological functions. So in ID, other iron-dependent functions, such as those involved in the central nervous system and immune function, are deleteriously affected before erythropoiesis is compromised and IDA becomes apparent. The prevalence of ID is significantly higher than IDA, particularly in women. ID is associated with a range of clinical outcomes including depression, reduced endurance and work performance, and compromised intellectual and cognitive functions.

In the brain, iron is predominantly located in the oligodendrocytes, microglia and astrocytes. The distribution of iron in the brain changes during the lifecycle; iron deprivation at different stages of development may result in irreversible changes [9], an important aspect when considering iron status of women of reproductive age.

Although brain iron normally accumulates throughout life, uptake of iron by the brain is tightly regulated. The blood brain barrier expresses TfR1 and iron is transferred from the endosomes to astrocytes. Neurons have a very high demand for energy so the brain is particularly susceptible to fluctuations in iron availability [10]. Although ID does not seem to result in increased expression of TfR1, the cycling rate of endosomes trafficking the Tf-TfR1

complex across the blood brain barrier is increased indicating that the rate of iron uptake into the brain is increased. Brain iron is important for establishing brain morphology in early life and is involved in several other roles such as myelination of nerves, synthesis of neurotransmitters such as dopamine, noradrenaline, serotonin and GABA, neurotransmitter metabolism and brain metabolism throughout life.

There is a clear relationship between iron levels and cognitive functioning (spatial ability, attention, memory, learning, reasoning ability and executive functioning) [11]. ID in women is associated with psychological effects and decreased dopamine production, affecting perception, motivation, memory, addiction and motor control. Iron supplementation in intervention studies frequently results in improved cognitive function and iron supplementation in pregnancy has been demonstrated to have effects on the offspring's cognition. In adult ID, iron therapy restores brain function [12] whereas ID in children may have irreversible detrimental consequences for the developing brain.

Iron overload and toxicity

As well as being essential for vital biological processes, iron can be damaging to the body. In the Fenton reaction, free iron in the presence of H_2O_2 and O_2 forms highly reactive and destructive hydroxyl radicals. These are important in the oxidative burst in neutrophils but can cause oxidative damage to essential macromolecules such as DNA, lipids, proteins and antioxidants. Iron overload leads to genetic instability and altered risk of infection and disease; excess iron is associated with diabetes, cardiomyopathy, liver damage, neurodegenerative diseases and various types of cancer.

Factors influencing iron status

Dietary quality affects absorption of non-heme iron from the gastrointestinal tract. Various dietary factors affect the availability of iron for transport; the net effect of the inhibitors and enhancers of iron absorption can be used to describe the dietary quality in terms of high or low bioavailability.

Ascorbic acid is the best dietary enhancer of iron absorption. The mechanisms involved include reducing ferric to ferrous iron in the lumen of the gastrointestinal tract, facilitating the release of iron from the food matrix during the gastric phase of digestion, increasing iron solubility in the small intestine, competing with phytates and polyphenols for iron binding and/or affecting intestinal barrier function. It should be noted that ascorbic acid is a particularly labile vitamin which is degraded by light, high temperature and oxygen.

An as yet unknown factor present in extracts of animal tissue such as meat, poultry and fish ('meat-fish-poultry factor') also enhances non-heme iron absorption [13]. The active factor may be particular amino acids or peptides and dietary fatty acids have also been demonstrated to affect iron absorption.

Dietary phytate (hexakisphosphate) and the closely related pentakisphosphate, which are found in cereals and legumes, have a significant impact on iron status because they bind iron tightly so the fraction of iron absorbed from the meal is markedly decreased. Whereas processing methods such as dehulling can reduce the amount of phytate in cereal grains, phytate is more evenly localized in legumes, seeds and nuts [14]. Non-ruminant species such as humans do not produce endogenous gastric phytase but foods can be treated with phytase to degrade dietary phytate and increase iron absorption.

Polyphenols, present in tea, cereals, fruits and vegetables, also inhibit the absorption of non-heme iron (and other metals) in a dose-dependent manner [15] and can be considered to be antinutrients. Some polyphenols can also bind to digestive enzymes and other proteins affecting their activity. Processing cereals reduces the concentration of polyphenols and enhances mineral bioavailability and the use of oxidizing agents is also partially effective.

Divalent ions such as zinc and manganese competitively inhibit iron absorption by DMT-1, however, the effect of calcium inhibiting iron absorption may be via an independent mechanism possibly by affecting the proton gradient which drives DMT-1. These effects are probably most significant when the sources of the minerals are supplements rather than foods.

The most effective way of promoting iron absorption is to consume iron with ascorbic acid-rich sources and avoid the consumption of polyphenols and other inhibitors in a meal which provides a significant source of iron. The use of dietary patterns rather than identifying single or limited combinations of nutrients or foods is a newly emerging method to investigate dietary intake and iron status. This novel approach, which uses factor analysis and logistic regression, has demonstrated that dietary patterns characterized by either a low intake of meat and vegetables or a high intake of milk and yoghurt were associated with an increased risk of suboptimal iron status [16].

The physiological state of the individual significantly affects iron absorption and iron status predominantly by altering hepcidin concentration (Figure 5). When iron status is low, gut iron transport is up-regulated by increased expression DMT-1 and hepatic production of hepcidin is reduced so more absorbed iron is exported from enterocytes and released from macrophages into the circulation. Iron absorption increases during periods of growth and increased demand, such as pregnancy. However, in

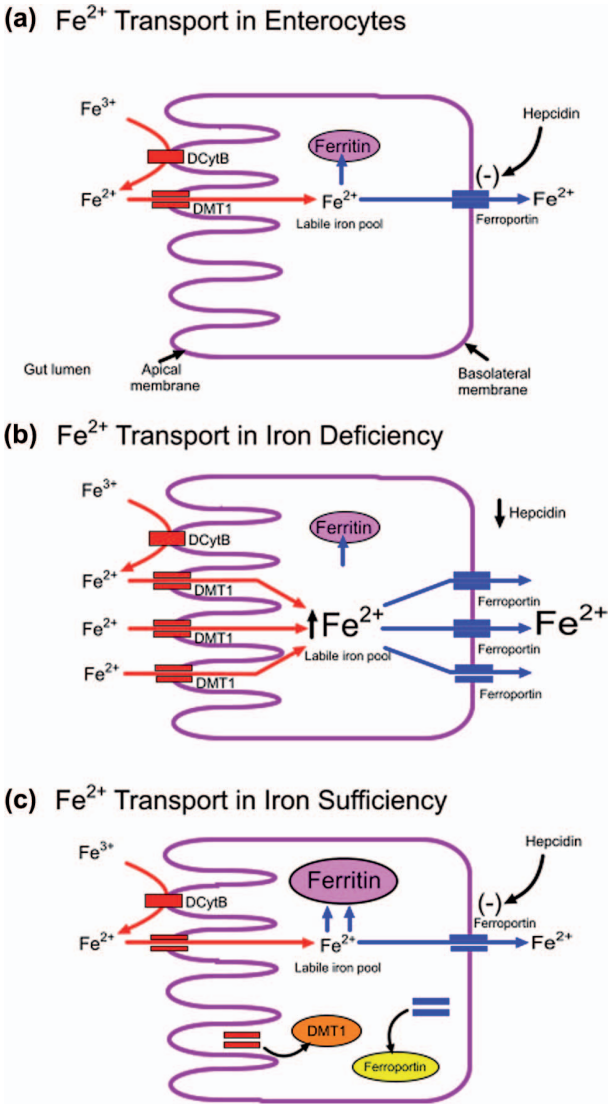


Figure 5. Regulation of iron absorption and uptake: (a) Iron is transported into the enterocytes by the divalent metal transporter (DMT1) and either stored in intracellular ferritin stores or exported out of the enterocyte by ferroportin. (b) When iron status is low, there is upregulation of gut iron transport primarily by an increased expression of DMT1. Also, under these conditions, release of hepcidin from the liver is reduced and more absorbed iron exported from the enterocytes and released from macrophages into the circulation. (c) In iron sufficiency, increased hepcidin production results in the internalization and degradation of ferroportin reducing export of iron from the enterocyte. The increase in intracellular iron results in internalization of DMT1 reducing the absorption of iron.

conditions in which inflammatory cytokines are increased, such as infection and inflammation, these mechanisms are overridden resulting in functional anemia. Functional anemia is characterized by iron loading in the tissues, because hepcidin levels are high, concurrently with paradoxical systemic anemia because iron export from cells and supply to the erythroid progenitor cells are curtailed.

In many parts of the world, deficiency of dietary iron is exacerbated by infectious diseases such as malaria, parasite infections, HIV/AIDs and tuberculosis. Malabsorption conditions such as coeliac disease and inflammatory bowel disease can affect the integrity of the cells lining the gastrointestinal tract and their ability to absorb nutrients as well as being associated with inflammation and increased hepcidin production.

The ability of the gut to up-regulate iron transporters is limited so high losses of iron can exceed the increased absorption. It is recommended that there should be an in-depth investigation of the gastrointestinal tract in individuals with unexplained anemia because gut lesions are the main reason for iron deficiency in men and postmenopausal women. These result in blood loss and are predominantly due to colon or gastric cancer and coeliac disease [17]. Use of non-steroidal anti-inflammatory drugs can also cause gastric bleeding and have significant impact on iron status. Infection with *Helicobacter pylori* is associated with ID and IDA because it both impairs iron uptake and increases iron loss; characteristically, the anemia is refractory to treatment with iron therapy but improves after eradication of the pathogen. In premenopausal women, high menstrual blood loss is one of the most common causes of IDA. Blood donation, particularly if it is frequent, is also likely to present a challenge particularly to smaller women consuming poorer diets whose iron status before donation is likely to be lower. Current practices by blood transfusion services identify potential donors with IDA but are usually not adequate to detect ID in donors who have normal hemoglobin concentrations.

Assessment of iron status

The standard assessment of IDA is to measure hemoglobin status which identifies late stage iron deficiency affecting erythropoiesis. However because production of red blood cells requires several other nutrients in addition to iron, hemoglobin concentration lacks specificity as a marker of ID. Measurement of hemoglobin concentration also has low sensitivity since hemoglobin synthesis is preserved at the expense of other iron-requirements. Likewise, other markers of impaired production of red blood cells such as mean cell hemoglobin concentration (MCHC), mean cell volume (MCV), red cell distribution width (RDW) and erythrocyte/zinc protoporphyrin also indicate late stage ID when there is not adequate iron for normal erythropoiesis. Increased RDW indicates coexisting deficiencies of folate and vitamin B12.

Identifying ID before IDA occurs is important in assessing individuals at risk or offering timely treatment. ID can be detected by assessing markers of iron in transport and indicators of increased demand by cells such as a fall in transferrin saturation and/or an increase in sTfR because cells express more TfR.

Classically mild iron deficiency (stage 1) is diagnosed by a fall in serum ferritin which reflects iron storage. However conditions, such as inflammation, which increase hepcidin production cause iron to be sequestered in cells so serum ferritin concentrations increase independently of iron status and could suggest iron stores are sufficient when there is actually a deficiency of iron. It is therefore essential to measure an inflammatory marker such as C-reactive protein concurrently. The growing prevalence of obesity may also limit the usefulness of serum ferritin as a biomarker because it is associated with increased cytokine and hepcidin secretion. Serum ferritin levels are also affected by malignancy, liver disease and alcohol consumption.

Serum sTfR is a useful marker of ID [18]; it is not an acute phase reactant like ferritin so it is not affected by inflammation and it increases with ID before IDA becomes manifest. Combinations of biomarkers such as the sTfR-ferritin index are also valuable in identifying ID before IDA, particularly where inflammation may coexist.

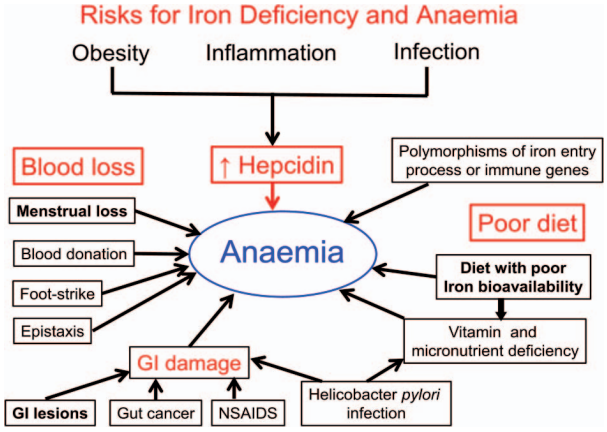


Figure 6. Contributors to iron deficiency and anemia. Blood loss can exceed the ability of the gut to upregulate iron absorption. In women of reproductive age, high menstrual blood loss is the most significant contributor to iron deficiency. In men and older women, blood loss from the gastrointestinal tract is the most common cause of iron deficiency. Diets of low iron bioavailability can reduce iron absorption. Factors, including obesity, that cause raised hepcidin concentrations compromise iron export and limit iron available for erythropoiesis.

Consequences of iron deficiency

ID is associated with a range of clinical outcomes including depression, reduced endurance and work performance, and compromised intellectual and cognitive functions [19]. Poor iron status has been associated with symptoms such as apathy, irritability, depression, fatigue and problems with concentration.

ID is not associated with a decrease in the oxygen carrying capacity of the blood but there is a fall in the iron-dependent dehydrogenases involved in substrate oxidation and in cytochromes which are involved in the electron transfer chain. This means that whereas ID affects endurance, energetic efficiency, aerobic adaptation, metabolic responses and muscle fatigue, IDA also affects aerobic capacity. IDA results in reduced maximal oxygen consumption (VO2 max) so aerobic physical fitness and endurance capacity are compromised, affecting physical performance and work tolerance. Both ID and IDA affect work productivity, voluntary activity (observed as an increase in sedentary behavior), fatigue and athletic performance. When iron supplements are given to individuals who have ID (reduced iron stores) but normal hemoglobin concentrations, an improvement in fatigue is reported because the synthesis of the iron-dependent enzymes involved in substrate metabolism and the electron transfer chain is increased.

Causes of iron deficiency

Iron deficiency (Figure 6) can be caused by a primary lack of dietary iron or poor iron bioavailability from a diet which has a high level of inhibitors. Diets which have low bioavailability are more likely to be those which are high in cereals and legumes and low in meat and fruit. Conditions which result in raised hepcidin limit availability of iron to pathogens but also to host cells and tissues for biological functions. This is advantageous for acute infections but chronic conditions can lead to severe and sustained iron deficiency. The escalating prevalence of obesity, a chronic inflammatory condition, also has the potential to compromise iron status. Although DMT-1 can be up-regulated to enable an increased absorption of dietary iron, the extent of possible compensation is relatively small. It is not possible for continual and sustained iron losses to be matched by increased iron absorption.

Conclusion

Women are particularly at risk of iron deficiency because the up-regulation of iron absorption is limited and may not be enough to compensate for iron lost during menstruation. Any additive factor affecting iron balance such as impaired iron absorption, inflammatory conditions, increased blood loss or increased demands such as closely spaced pregnancies can result in a loss of iron that cannot be compensated for by increased absorption. However excess iron may result in oxidative damage or favor the growth of pathogens; indeed it has been suggested [20] that evolutionary pressures have resulted in the development of an iron deficiency human phenotype which protects against infectious diseases; this might offer an explanation for the ubiquitous persistence of ID worldwide despite improved nutrition and medicine.

The concern is that consequences of ID may be overlooked if an inappropriate biomarker such as

hemoglobin is used as the sole indicator of iron status. The negative impact of ID on various functions of the brain is becoming increasingly apparent. Emerging research indicates that the role of iron in various neuronal functions including signal transduction, myelination, dendritic arborization, synaptogenesis and plasticity results in ID affecting cognitive function, particularly memory and learning. Some of the neurological consequences of ID appear to persist even after the iron status is restored. Women have a greater risk of ID and IDA and thus are more prone to the deleterious impact these conditions could have on the function of the central nervous system.

Questions and answers

Q (Gronowski): May iron deficiency perhaps prevent infectious diseases?

A (Coad): It probably doesn't prevent infectious diseases but survival may be better. It is likely that historical procedures, such as blood-letting, worked by reducing the infectious load.

Q: Are specific nutritional recommendations given to blood donors who donate every 6 months?

A (Coad): It is a lost opportunity in many countries that advice is not given.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Trumbo P, Yates AA, Schlicker S, Poos M. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. J Am Diet Assoc 2001;101: 294–301.

[2] McKie AT. The role of Dcytb in iron metabolism: an update. Biochem Soc Trans 2008;36:1239–41.

[3] Anderson GJ, Vulpe CD. Mammalian iron transport. Cell Mol Life Sci 2009;66:3241–61.

[4] Ganz T. Cellular iron: ferroportin is the only way out. Cell Metab 2005;1:155–7.

[5] Ganz T. Systemic iron homeostasis. Physiol Rev 2013;93: 1721–41.

[6] Skaar EP. The battle for iron between bacterial pathogens and their vertebrate hosts. PLoS Pathog 2010;6:e1000949

[7] Ganz T, Nemeth E. Iron sequestration and anemia of inflammation. Semin Hematol 2009;46:387–93.

[8] Zimmermann MB. Methods to assess iron and iodine status. Br J Nutr 2008;99(Suppl. 3):S2–9.

[9] Fretham SJ, Carlson ES, Georgieff MK. The role of iron in learning and memory. Adv Nutr 2011;2:112–21.

[10] Morris CM. Any old iron? Brain 2011;134:924–7.

[11] Munoz P, Humeres A. Iron deficiency on neuronal function. Biometals 2012;25:825–35.

[12] Beard JL, Connor JR. Iron status and neural functioning. Annu Rev Nutr 2003;23:41–58.

[13] Hurrell RF, Reddy MB, Juillerat M, Cook JD. Meat protein fractions enhance nonheme iron absorption in humans. J Nutr 2006;136:2808–12.

[14] Beal L, Mehta T. Zinc and phytate distribution in peas: influence of heat treatment, germination, pH, substrate, and phosphorus on pea phytate and phytase. J Food Sci 1985;50:96–100.

[15] Perron NR, Brumaghim JL. A review of the antioxidant mechanisms of polyphenol compounds related to iron binding. Cell Biochem Biophys 2009;53:75–100.

[16] Beck KL, Kruger R, Conlon CA, Heath AL, Matthys C, Coad J, Stonehouse W. Suboptimal iron status and associated dietary patterns and practices in premenopausal women living in Auckland, New Zealand. Eur J Nutr 2013;52: 467–76.

[17] Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. Gut 2011;60:1309–16.

[18] Koulaouzidis A, Said E, Cottier R, Saeed AA. Soluble transferrin receptors and iron deficiency, a step beyond ferritin. A systematic review. J Gastrointest Liver Dis 2009;18:345–52.

[19] McClung JP, Murray-Kolb LE. Iron nutrition and premenopausal women: effects of poor iron status on physical and neuropsychological performance. Annu Rev Nutr 2013; 33:271–88.

[20] Denic S, Agarwal MM. Nutritional iron deficiency: an evolutionary perspective. Nutrition 2007;23:603–14.