Iron metabolism

Deirdre Conway
Mark A Henderson

Abstract

Iron is a key micronutrient and has a vital role in oxygen transport through its presence in haemoglobin and a key part in oxidative phosphorylation via electron transfer in cytochromes. Total body iron is approximately 4000 mg in a 70-kg man. This goes through a continual cycle of conservation and re-utilization. Syndromes of iron deficiency and overload arise from aberrancy within the steps of iron metabolism.

Keywords Iron; iron handling; physiology

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article, you should:

- understand the distribution of total body iron
- be able to describe how iron is absorbed, cycled and stored
- understand the role of iron in haemoglobin

Iron is an essential micronutrient with a number of vital roles in oxygen transport, oxygen storage, enzymatic function and energy generation. In a typical 70-kg man, total body iron is approximately 4000 mg.[1] Sixty-five per cent of total body iron is found in haemoglobin, 10% in myoglobin (within muscle fibres) and other tissues, with the remainder stored within the liver, bone marrow and macrophages[2] (Figure 1)

Sources of iron

Iron is not synthesized within the body and therefore must be absorbed from dietary sources. A typical adult diet contains 10–15 mg elemental iron, with 10–20% of this being absorbed.[3] The recommended daily allowance of iron is shown in Box 1. Dietary sources include lean red meat, liver, eggs and spinach. Iron from fruits, vegetable and grains is harder for the duodenum to absorb.

Iron handling

Iron absorption

There is no physiological mechanism by which an excess of total body iron (TBI) may be excreted. Consequently, TBI is regulated thorough the precise control of dietary iron absorption,[1] with the duodenum acting as the principle site of absorption. A loss of approximately 1–2 mg of iron occurs daily due to the sloughing of cells from the enteric mucosa, desquamation of skins cells, and from the formation of sweat and urine.[1] This loss is matched by a daily absorption of 1–2 mg. However, this represents only a small proportion (7–20%) of the total daily dietary intake. Physiological conditions that cause increased iron loss (e.g. menstruation, lactation) may be balanced with an absorption of up to 3 mg per day.[3]

Dietary iron is presented to the intestinal mucosa in the form of both haem iron and elemental (non-haem) iron. Haem iron is that which is contained within haemoglobin and myoglobin of animal tissue and is absorbed much more readily than elemental iron, although its exact mechanism of absorption is uncertain.[1,4] The haem carrier protein-1 (HCP-1) that had initially been thought to be the means of haem iron absorption into the duodenal enterocyte[3] has since been correctly identified as a folate transporter.[1]

Elemental iron exists in two valency states – the reduced ferrous (Fe^{2+}) state and the oxidized ferric (Fe^{3+}) state.[1] Elemental iron can only be absorbed by the duodenal enterocytes in its ferrous state.[3] Any elemental iron in the ferric state must be reduced by duodenal cytochrome b (also called cytochrome b reductase 1), which is present on the apical membrane of duodenal enterocytes.[3] The resulting ferrous iron can then be taken into the cytoplasm of the duodenal cell by the divalent metal ion transporter-1 (DMT-1).[3] The uptake of elemental iron requires acidic conditions to aid the solubility of ferrous iron and to provide protons for co-transport via the DMT-1.[1] Once the ferrous iron has been absorbed into the enterocyte cytoplasm it may be utilized in one of three ways. Firstly, it may be transferred to local mitochondria to produce haem molecules. Secondly, it may be transferred into ferritin and then stored within the enterocyte. Thirdly, it may be removed from the cell to be transported to distant body sites.[1] To be released as circulating iron, ferrous iron is exported from the enterocyte by the transporter molecule ferroportin, which is found on the basolateral membrane.[4] Ferroportin is also present on reticuloendothelial macrophages.

The rate of iron absorption in the duodenum and the release of iron to the circulation is regulated in order to meet the systemic demands for iron.[5] The hormone hepcidin, a small peptide molecule released from the liver, is chiefly responsible for this. Hepcidin is released when the bodily stores of iron are adequate or high, as detected by the liver iron stores and circulating iron

Recommended daily allowance of iron

Man ≥19 years	8.7 mg
Woman 19–50 years	14.8 mg
Woman ≥50 years	8.7 mg
(100 g cooked red meat contains 0.5–3 mg iron)	

Box 1

Deirdre Conway *MBChB FRCA is a Specialty Registrar in Anaesthesia at Glasgow Royal Infirmary, Glasgow, UK. Conflicts of interest: none declared.*

Mark A Henderson *FRCA MAcadMEd FFICM MRCP(UK) is a Specialty Registrar in Anaesthesia and Intensive Care Medicine at Queen Elizabeth University Hospital, Glasgow, UK. Conflicts of interest: none declared.*

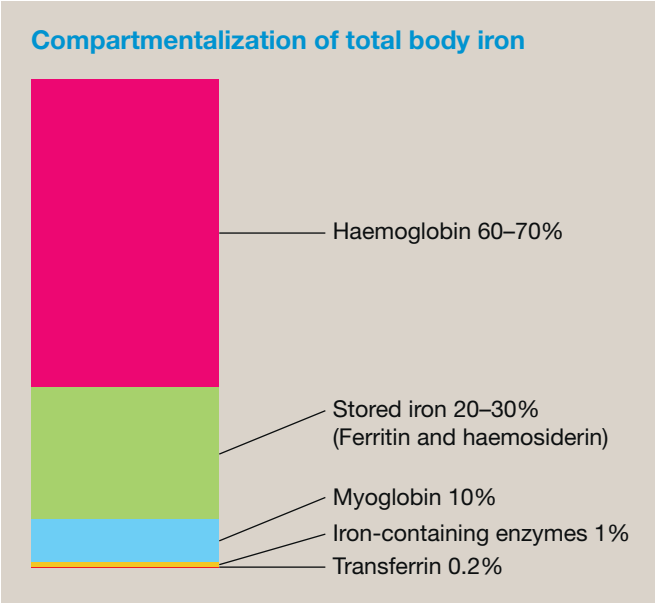

Figure 1

levels.[4] Its mechanism of action is to block iron release to the circulation by degrading the ferroportin transporter, of both duodenal enterocytes and reticuloendothelial macrophages.[5] Consequently, the iron these cells contain becomes sequestered within each cell. Enterocytes experience a rapid turnover; the iron sequestered within them will be lost as they are rapidly shed from the enteric mucosa, thereby reducing the duodenal absorption of iron.[1] Hepcidin may further reduce duodenal iron absorption by impeding DMT-1 transcription at the enterocyte.[1]

Hepcidin is an acute phase protein that is also expressed under conditions of infection and systemic inflammation in response to cytokines, principally interleukin-6.[4,5] This host response to infection limits the amount of circulating iron available to any invading pathogen. Through this response, hepcidin is responsible for the iron sequestration seen in the anaemia of chronic disease.[5] Hepcidin expression is down-regulated by increased red blood cell production (erythropoiesis), iron deficiency and tissue hypoxia.[5]

Iron transfer mechanisms

Iron is a highly reactive element. Consequently, a system of organic molecules must bind free iron so that it can be transferred and stored without causing cellular damage from the formation of reactive oxygen species.[4] Apotransferrin is a glycoprotein that binds free iron, forming the molecule transferrin, which is the means of transporting circulating iron in the plasma.[1] It binds iron that is released to the systemic circulation from duodenal enterocytes and macrophages.[5] Transferrin supplies the erythroblasts in the bone marrow with circulating iron for erythropoiesis. It supplies the tissues that require iron for growth and reparative processes.[1] It also supplies the iron that binds to the storage molecules ferritin and haemosiderin.

The iron cycle

Total body iron undergoes a continual cycle of conservation and re-utilization. Although only 1–2 mg is absorbed each day, iron is continually released from the haem molecules of senescent reticulocytes that are broken down by phagocytosis in the spleen. The reticuloendothelial macrophages that perform this process turn over approximately 30 mg of iron daily.[1] These iron-containing macrophages constitute a large, dynamic iron reservoir that is regulated by the hormone hepcidin.[4]

Iron storage

Iron is stored in its ferric (Fe^{3+}) state, bound to either ferritin or haemosiderin. Ferritin is a ubiquitous protein, common to all body cells. For this reason, every cell can store ferric iron intracellularly. The predominant storage sites are the liver (25%), spleen and bone marrow. Ferritin is a large protein molecule of 480 kDa with a maximum binding capacity of 4500 ferric iron atoms per ferritin molecule. However, each molecule of ferritin typically binds less than its maximal capacity (approximately 2000 ions). Ferritin is a soluble complex that is easily mobilized, and constitutes two-thirds of the stored iron within the liver. One-third of iron stores within hepatocytes are bound to haemosiderin, which is a degraded form of ferritin and is relatively insoluble and slow to mobilize.[1]

Iron and cytochromes

Iron plays a key role in oxidative phosphorylation and ATP generation due to its presence in cytochromes. Cytochromes are haem containing proteins that utilize electron transfer to alternately oxidize and reduce the iron component. In oxidative phosphorylation, the flow of electrons is coupled to ATP production.[6]

Iron and haemoglobin

Iron is a key component of the haem moiety of the haemoglobin molecule. Haem consists of an organic portion (a protoporphyrin ring) surrounding a central iron ion (in the ferrous state, Fe^{2+}). The Fe^{2+} ion forms six bonds in total within haem-four to nitrogen atoms with the protoprophyrin ring, one to a histidine residue on an alpha-globin chain and the final bond made to oxygen as needed.[7]

Haem is synthesized both in the cytosol and the mitochondria of erythrocytes. A haemoglobin molecule consists of four polypeptide globin chains (two alpha, two beta in HbA) with each chain surrounding a haem moiety (Figure 2); 95% adult haemoglobin is HbA.

The main function of haemoglobin is the transport of oxygen from lungs to tissues. Its secondary functions include carbon dioxide carriage and buffering of hydrogen ions in the erythrocyte.

Iron overload

Disorders of iron overload may arise from deficiencies with the hepcidin–ferroportin axis (e.g. hereditary haemochromatosis), erythoid dysfunction (e.g. iron overload anaemias) and impaired iron transport (e.g. hypotransferrinaemia, a rare autosomal recessive condition).[4]

Untreated, iron excess in tissues can lead to multi-organ deposition and failure. The mainstays of treatment include venesection (in disorders without anaemia such as haemochromatosis) and chelation therapy (in iron overload anaemias such as thalassaemia).

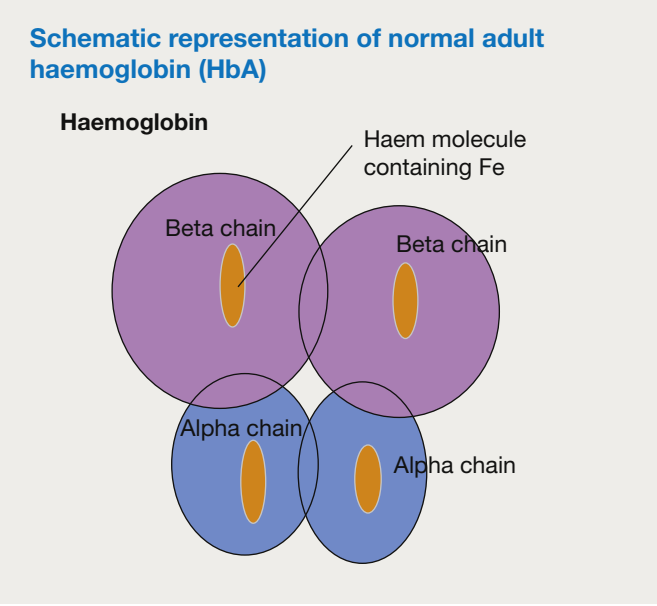

Figure 2

Iron deficiency anaemia

The causes of iron deficiency are multitude and broadly encompass increased demand (e.g. childhood growth), increased loss (e.g. gastrointestinal bleeding) and decreased supply (e.g. poor dietary intake).[8] Chronic iron deficiency can lead to a syndrome of iron deficiency anaemia.

Iron deficiency may be highlighted at preoperative assessment of a patient for surgery with optimization of iron status considered. A full review of iron deficiency and perioperative management is beyond the scope of this article. A recent international consensus statement on management of perioperative anaemia has informed our recent practice.[2] ◆

REFERENCES

1 Scientific Advisory Committee on Nutrition. Iron and health. 2010. London: The Stationery Office. Also available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/339309/SACN_Iron_and_Health_Report.pdf (accessed 30 June 2018).

2 Munoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* 2017; **72**.

3 Winter WE, Bazydlo LAL, Harris NS. The molecular biology of human iron metabolism. *Lab Med* 2014; **45:** 92–102.

4 Fleming R, Ponka P. Iron overload in human disease. *N Engl J Med* 2012; **366:** 348–59.

5 Camaschella C. Iron-deficiency anemia. *N Engl J Med* 2015; **372:** 1832–43.

6 Yentis SM, Hirsch N, Smith GB. Anaesthesia and intensive care A-Z: an encyclopaedia of principles and practice. Fifth edition. Edinburgh: Churchill Livingstone, 2013.

7 Thomas C, Lumb AB. Physiology of haemoglobin. *Cont Educ Anaesth Crit Care Pain* 2012; **12:** 251–6.

8 Muñoz M, García-Erce JA, Remacha AF. Disorders of iron metabolism. Part II: iron deficiency and iron overload. *J Clin Pathol* 2011; **64:** 287–96.