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REVIEW ARTICLE

Iron deficiency anaemia

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Abstract Iron deficiency anaemia is a public health problem that affects all age groups. In Mexico, it is a common cause of morbidity, and accounts for 50% of cases of anaemia worldwide. It is more prevalent during the first 2 years of life, during adolescence and pregnancy. It is characterised by fatigue, weakness, pallor and koilonychia. Treatment is based on dietary recommendations and oral and intravenous iron supplements. In this review article, we summarise the characteristics of iron efficiency anaemia, its metabolism, epidemiology, symptoms and diagnosis, and explore different therapeutic approaches.

PALABRAS CLAVE
Anemia ferropénica;
Compuestos férricos;
Revisión de la utilización de medicamentos;
Trastornos del metabolismo del hierro

Anaemia por deficiencia de hierro

Resumen La anemia por deficiencia de hierro, es un problema de salud público, ocurre en todas las etapas de la vida. En México es una causa frecuente de morbilidad, y representa el 50% de casos de anemia a nivel mundial, es más frecuente durante los 2 primeros años de vida, la adolescencia, mujeres embarazadas. Se caracteriza por presentar fatiga, debilidad, palidez de tegumentos, coloiniquia; el tratamiento se basa en recomendaciones dietéticas, suplementos de hierro vía oral y vía intravenosas. El presente artículo de revisión se resume las características de la anemia por deficiencia de hierro, metabolismo, epidemiología, cuadro clínico, diagnóstico y alternativas terapéuticas.

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Background

Metabolism of iron

Iron is the second most abundant metal in the earth's crust, and is essential for life. It is a vital component of several bodily functions, primarily haemoglobin synthesis and transport of oxygen throughout the body. It is found in several different enzymes involved in maintaining cell integrity, such as catalases, peroxidases and oxygenases. Proportionally higher concentrations of iron are found in the basal ganglia of the human brain than in liver. In breastfeeding infants, parts of the brain, particularly the microglia, continue to develop, and therefore iron is vital for developing cognitive functions at this stage of life.[1,2]

In the body, iron is distributed in 2 compartments. The first is a functional compartment formed of a number of compounds, including haemoglobin, myoglobin, transferrin and enzymes, and all of which require iron as a cofactor or a prosthetic (ion or haem) group. The second is a storage compartment, formed of ferritin and haemosiderin, which constitute the body's mineral reserves.[2] The body iron content of a normal, 70 kg individual is around 50 mg/kg; 3.5–4 g in women, and 4–5 g in men. Most of the iron is distributed as follows: 65% in haemoglobin (2300 mg), 15% in myoglobin and enzymes, 20% in iron stores, and only 0.1–0.2% is bound to transferrin (Fig. 1).[2,3]

Absorption of iron

A normal diet contains 6 mg/1000 calories, with a daily intake of 15–20 mg of iron absorbed in the duodenum and the first part of the jejunum (1–2 mg/day). Iron is found in 2 forms: haem (10%) and non-haem (90% ionic). Haem iron is found in foods of animal origin (red meat, chicken, fish) in the form of haemoglobin or myoglobin; between 15% and 20% of haem iron is absorbed. Non-haem, or inorganic, iron is found in foods of plant origin, cereals, and some foods or animal origin such as milk and eggs; less than 5% of non-haem iron is absorbed.

Haem is most easily absorbed form of iron: through a process called endocytosis, iron is taken up directly by intestinal cells, where haem oxygenase (hox) breaks its ring to release ferrous iron (Fe^{2+}).

Dietary non-haem or inorganic iron is found as an oxide (Fe^{3+}). The apical edge of the enterocyte contains a ferric reductase enzyme (duodenal cytochrome B [Dcytb]), which transforms ferric iron (Fe^{3+}) to its soluble ferrous iron (Fe^{2+}) form, thereby allowing it to pass through the mucous membrane of the intestine. Non-haem iron is transported by a protein called divalent metal transporter 1 (DMT1), which also carried other metallic ions such as zinc, copper and cobalt by means of a proton coupling mechanism. In the enterocyte, iron can follow 2 pathways: a small ferritin-bound portion is stored; the rest is transported through the basolateral membrane of the enterocyte by ferroportin 1 (Ireg-1), aided by the protein hephaestin, which transforms Fe^{2+} into Fe^{3+}. Thus released, it passes into the systemic circulation and binds with transferrin. Enterocytes can also take up iron from the blood by means of transferrin receptor 1 (TfR), expressed on its basolateral membranes, in association with HFE (also called the hemochromatosis gene) and β2 microglobulin (Fig. 2).

Non-haem iron absorption is strongly influenced by dietary factors, such as meat or ascorbic acid (vitamin C), which improve the bioavailability of non-haem iron. A diet containing calcium (dairy products), tannins (tea), or phytates (fibre-rich diets), meanwhile, together with the administration of medicines such as tetracycline, proton pump inhibitors, and antacids, can diminish iron absorption.[3–5]

Systemic iron homeostasis

Hepcidin is currently thought to be the main regulator of systemic iron homeostasis, including the intestinal absorption of iron and the recycling of iron in the REC. Hepcidin is a 25-amino acid protein that binds to ferroportin, leading to internalisation and subsequent liposome degradation. As ferroportin is known to be an iron exporter, hepcidin traps iron in enterocytes, macrophages and hepatocytes (Fig. 3).[6]

Hepatic production of hepcidin is regulated by the degree of transferrin saturation and transferrin receptor (TfR) 1 and 2 levels in the liver. Therefore, an increase in the diferric Tf/TfR ratio induces hepcidin expression, which acts by inhibiting ferroportin-1 activity, and with it, basolateral iron transport. However, a decrease in the diferric Tf/TfR ratio halts production of hepcidin in the liver, and iron absorption is restored.

Distribution of iron

Once absorbed, the iron enters the blood stream and binds to Tf for transport. The hepatic synthesis of Tf is regulated by intracellular iron, so that when iron levels decrease, plasma transferrin levels increase. Tf can bind up to 2 iron atoms, and therefore the transferrin saturation index (TSI) is usually around 30–35%. The TSI is involved in regulating erythropoiesis, and this is drastically reduced when the TSI falls below 16%. In contrast, when the TSI increases to over 90%, iron transported by Tf is diverted to the liver, and can cause hepatic haemosiderosis.

TfR, DMT-1 and ferritin synthesis in erythroblasts is inversely regulated by iron regulatory proteins 1 and 2 (IRP1 and IRP2). Therefore, iron erythroblast uptake is increased by increasing TfR production and reducing ferritin production, and vice versa (Fig. 4).

EPO has been shown to activate IRP-1 during erythropoiesis, causing TfR overexpression in erythroid progenitors. This continues during differentiation, and is mediated by transcriptional and post-transcriptional mechanisms.[6,7]

Iron storage and recycling

One hundred and twenty days after entering the circulation, senescent erythrocytes are phagocytised by macrophages in the spleen, liver or bone marrow, where haem oxygenase breaks down the haem group and releases Fe^{2+}, which is transported by Nramp-1 into the cytoplasm. A significant proportion of this iron will be stored in the macrophage as haemosiderosis and ferritin, while the rest is transported