New findings on iron absorption conditioning factors

Novos achados sobre os fatores condicionantes da absorção do ferro

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Abstract *The authors focus iron intake regulation in the body and the probable mechanisms related to iron absorption. They analyze the impact of iron absorption deficiency resulting in iron deficiency anemia, a public health issue of great impact in the world influencing child and maternal health risk increase. This paper aims at highlighting the problems affecting the uptake or inhibiting processes of iron absorption in an attempt to correlate information on conditioning factors and current findings. This study is a document based descriptive study comprising literature review. In food, iron has different forms, such as the heme and non-heme forms following different absorption pathways with different efficiency rates, depending on conditioning factors, such as diet profile, physiological aspects, iron chemical state, absorption regulation, transportation, storing, excretion and the presence of disease, They also discuss the current difficulties in dealing with iron nutritional deficiency in vulnerable groups, children and pregnant women, and focus data on iron consumption, adhesion to breast feeding and the frequency of prenatal care visits.*

Key words *Iron, Biological transport, Hematinics, Absorption, Anemia, iron deficiency*

Resumo *Os autores abordam a regulação da entrada de ferro no organismo e os prováveis mecanismos que permeiam essa regulação. Analisam o impacto da deficiência de absorção de ferro que acarreta anemia ferropriva, que se constitui hoje num problema de saúde pública de grande repercussão e, é reconhecidamente, a doença de maior magnitude em âmbito mundial, concorrendo com elevação de riscos à saúde materna e infantil. O objetivo do trabalho é ressaltar os problemas que afetam o processo de captação ou inibição da absorção do ferro, buscando correlacionar os conhecimentos sobre os fatores condicionantes e os achados atuais. O estudo foi do tipo descritivo, de base documental, compondo uma revisão de literatura. Nos alimentos, o ferro se encontra em formas diferentes, ferro heme e não heme as quais seguem distintas rotas de absorção com diferente eficiência, na dependência de condicionantes, como perfil dietético, aspecto fisiológico, estado químico do ferro, regulação da absorção, transporte, armazenamento, excreção e a presença de doenças. Discutem também a atual dificuldade de enfrentamento da carência nutricional de ferro em grupos vulneráveis, crianças e gestantes, e enfocam dados sobre consumo alimentar de ferro, adesão ao aleitamento materno e freqüência ao pré-natal.*

Palavras-chave *Ferro, Transporte biológico, Hematínicos, Absorção, Anemia ferropriva.*

Introduction

The value of iron for living beings goes back to the XVII and XVIII centuries when iron metabolism systematic study was established with the discovery of the hemoglobin specter and observation of erythrocytes in the tissues. Modern studies are using radioisotopes in clinical and experimental investigations of iron metabolism and its role in the organism.[1] Nevertheless, the recognition of the benefits credited to the role of iron in the metabolism has preceded modern times in many centuries according to historical documents inherited from the Egyptians, Greeks, Romans and Chinese.[1]

Anemias caused by different nutritional deficiencies is nowadays a severe public health issue, and iron deficiency anemia occurs in a greater scale as compared with the other types and is recognized as one of the more prevalent diseases in the world. It is estimated that approximately 2.15 billion people are affected by the disease.[2]

Based on the estimate prevalence of hematocrit and hemoglobin levels, anemia is rated severe when prevalence is equal or over 40%. Anemia prevalence from 1990 to 1995 was also estimated based on hemoglobin concentration for non-industrialized countries in: 39% for children from zero to four years old; 48.1% for children from five to 14 years old, 52.0% for pregnant women and 42.3% for all women.[3]

More recent studies performed in Brazil, although they do not as a whole refer to the population base for lack of representative samples, have documented high levels of iron deficiency anemia contributing to morbidity and mortality risks for children and mothers, low work and mental productivity and learning impairment among other factors.[4-6]

Iron intestinal absorption through the brush border of intestinal mucous cells (enterocytes) following availability in the digestive process is principally located in the small intestine, the principal site for iron absorption in larger concentration in the duodenum followed by the proximal jejunum and in a smaller degree in the more distal portions of the small intestine.[7-10] Aspects impacting iron metabolism processes have been permanently focused by scientific researches aiming at breaking through the current levels of knowledge related to mechanisms and factors conditioning iron absorption and regulation.

The objective of this study is to highlight problems affecting iron uptake or inhibiting the absorption process through the correlation of conditioning factors and current findings.

The study is a document based descriptive study encompassing technical literature sources analysis and synthesis, scientific articles, international organizations'literature and Web research using the following key-words: iron deficiency anemia for reference to the Medline database, and anemia, deficiency, *hierro* in the Lilacs data system, comprising a literature review from March to August, 2003.

Metabolic aspects of iron absorption

Availability, composition and iron content in diet are the more important factors described for modulating iron absorption conditions in the organism.

Apoferritin synthesis performed by mucous cells is a mechanism of regular iron transference through the mucous-capillary interface. When the level of iron stored is high and consequently organic need is low the organism moves to increase the apoferritin synthesis. Apoferritin is a substance sequestering iron in the interior of the mucous cell inhibiting its transference to the capillary bed. Iron linked to the mucous cells, when periodic desquamation occurs, within a mean period of four to five days, is carried into the intestinal lumen. In a situation of iron deficiency apoferritin synthesis inhibition occurs and will not compete with the iron transference to an iron deficient organism.[7,8] This mechanism is known as mucous block and was postulated by Granick in 1954.[1,7,10]

To determine to what extent daily iron supplement can block the absorption of a subsequent dose, a comparative study of the effect of oral iron and intra-peritoneal iron administration *status* was performed in anemic rats. The efficiency of iron supplementation, measured after three days by means of liver storage indicated that oral supplementation is comparable to intra-peritoneal administration in terms of iron status increment. The authors concluded that there is mucous blockage with the administration of oral iron supplement, but the extent of the effect is not as dramatic as previously thought.[11]

New studies suggest that iron is assimilated by mucous cells in the form of low molecular weight complexes such as sorbitol and fructose. Therefore, iron could be transferred to apoferritin or form other low molecular weight quelants which in plasma would form a complex such as transferrin, a process known as the pathway theory.[1,7] In this matter authors have demonstrated that the replacement of glucose for fructose marked with ^{59}Fe in experiments with rats significantly increases iron retention and absorption. An increase also occurs in the presence of lactose but, not statistically significant. This finding does not discard the possibility of quelaton being the mechanism responsible for the iron absorption effect of fructose.[12]

Another proposition tries to explain iron duodenum absorption through the mucin - mobilferrin - intergrin pathway when mucin in the duodenal lumen may contribute to the solubilization process of ferric ions in acid pH keeping them available in the alkaline pH of the duodenum.[13,14] Iron presentation to integrin, a transmembranic protein, known as a cytosolic ligand facilitates iron transit through the microvillous of the duodenal membrane. Mobilferrin is a molecule that links to iron within the cell and regulates iron absorption sequestering it from its interior and making it available to transferrin when the organism is in need of iron.[8]

Notwithstanding the existing *consensus* that iron uptake regulation in the organism takes place in the small intestine cells, the precise mechanism of this regulation still remains under discussion.

Metabolic aspects related to iron storage, transportation and excretion

Iron contained in the heme structure of hemoglobin has the property of easily reacting through oxireduction playing an important role in pulmonary CO_2 elimination.[15]

Iron, globine and porfirin are essential to the synthesis of hemoglobin. Iron deficiency can be caused by the ingestion, absorption, transportation or inadequate biologic use or by excessive blood loss which leads to an abnormal heme synthesis causing anemia when hemoglobin blood concentrations are below levels considered normal.[15]

Ferritin, an iron storage protein existing in the form of individual molecules or an aggregate known as hemosiderin, is principally located in the liver as well as in the reticuloendothelial cells and in the bone marrow. Ferritin's basic function is to assure intracellular iron storage and posterior use in the protein and enzyme synthesis. Hemosiderin is chemically similar do ferritin from which it can be distinguished for not being water soluble.[7,16]

Iron is normally stored in two types of cells: liver macrophages, spleen, bone marrow and hepatic parenchimatous cells.[4] The quantity of iron stored varies within ample limits before physiological alterations can be detected. In the case of iron deficiency anemia, iron stocks are depleted. On the other extreme, hyperferremia with tissue lesions probabilities occurs when these rates are over approximately 20 times the average normal quantity.[7]

Iron is distributed in two principal *pools*: hemoglobin fundamental iron, mioglobin and iron enzymes stored in ferritin, hemosiderin and transferring.[7]

The presence of iron in the tissues presupposes the existence of transferrin in the plasma and specific receptors in the cell membrane of that protein. These receptors capture transferrin-iron in the cell surface transporting it to the interior of the cell where iron is released. Transferrin receptors have high iron affinity explaining their larger number in the precursor tissues of erythroids in the bone marrow, placenta and liver.[17]

Iron in the organism is submitted to a rigorous reuse system, stock control and strict loss limits in quantities varying from 1 to 2 mg/day. Iron in general is eliminated through cellular desquamation, especially in the gall, feces, urine and sweat or in the form of ferritin carried with the duodenal and jejunum mucus. This loss can be detected through electronic microscopy and X-Ray microanalysis.[7,18] In adults, approximately 90% to 95% of the iron required for hemoglobin synthesis originates from the recycling of destroyed erythrocytes.[7,16] Organic iron pools in children are going through a process of consolidation for they respond to growth and body development demands. The principal difference between iron metabolism in children and adults is the dependency that children have of the iron content in food.[16]

Principal iron absorption conditioning factors

Many factors condition iron uptake by the organism. Among them the most widely quoted are: a) iron chemical state; b) the role of iron reducers; c) specific protein co-factors, d) dissociation of iron ligands; e) gastrointestinal tract pathological processes.

Iron chemical status

Concerning investigations on the use of iron in food, Callender[19] emphasizes the superior capacity of iron absorption in meats stating that diversity in iron use of different sources could explain the development of nutritional anemia in cases where iron intake is considered adequate.

In inorganic food compounds, iron is normally in the oxidized form[7,18] but absorption requires reduction to Fe^{+2}, for iron enters in the mucous cell as a reduced free ion.[10] For reasons not yet clear, ferrous ion is more easily absorbed than ferric ion. In this condition the non-heme iron is abundantly found in vegetal sources. On the other hand, in the chemical state of heme iron, with intact ferriporfirin ring, iron enters the cell and is separated from the cytoplasmatic ring in the enterocyte.[8] Iron physical and chemical form affects its absorption as described by Conrad[20] who used radioactive markers and concluded that hemoglobinic iron is more efficiently absorbed than inorganic iron.

Heme iron is derived from the hemoglobin; mioglobin and transferrin of fowls and fish and in smaller scale of other animal sources. In this last state non-heme iron is found in a smaller proportion but absorption is greater because it's last affected by diet components.[7] Hematinic compounds have an absorption rate 15% or 30% higher than non-hematinic. Vegetal sources are the ones with lower iron absorption rates, varying from 0%-10%.[8,17]

The role of reducing agents

There are many differences in the absorption of iron in food. Diets rich in reducing agents, such as ascorbic acid, meat factor, sugar, amino acids containing sulfur form quelate with ionic iron increasing inorganic iron bioavailability.[7,15]

The available portion of any nutrient is the one effectively absorbed enabling its use by cellular metabolism. Nutrients contained in food immediately available in the organism following intake are extremely rare. Data on the bioavailability of vitamins and minerals in natural and processed food are still very scarce. Different vitamins and mineral form complexes with other vegetal and animal tissue components, particularly with proteins,[7] to a certain extent conditioning its biological use.

Iron has a greater bioavailability when present in the form of iron sulfate than in salts such as sulfite, bisulfate, phosphate, carbonate, bicarbonate among others.[7]

Cook e Reddy[21] have demonstrated that iron absorption in a more complete diet as compared with a simple meal did not differ significantly from the average iron absorption in three diet periods, notwithstanding the amount of Vitamin C uptake varying in the order of 51 mg to 247 mg. Nevertheless, absorbed values when adjusted to iron *status* differences of researched individuals, were positively correlated to ascorbic acid ($p = 0{,}01$) and animal tissue ($p = 0{,}03$).

Trace elements interaction in cereal based diets supplemented with iron, Vitamin A and beta-carotene demonstrated that Vitamin A increased iron absorption more than twice in rice, 0.8 in wheat and 1.4 in corn. Beta-carotene increased absorption over three times for rice and 1.8 times for wheat and corn suggesting that both components prevent phitate effects inhibition on iron absorption. [Nevertheless, although a progressive increase in Vitamin A and beta-carotene increases iron absorption, when a maximum threshold is reached this metabolic response ceases].[22]

Meat promotes non-heme iron absorption through the stimulation of gastric acid,[23] for the acid condition of the stomach concurrently causes the reduction of iron and helps absorption increasing availability. Nevertheless, heme-iron is minimally affected by meal content and gastrointestinal secretions to enter the lumen and get to the intestinal mucous cell and although its absorption can reach 25% compared to only 5% of the non-heme iron it represents only 5% to 10% of the iron in individuals consuming a varied diet.[7]

Specific protein co-factors

Bioavailability explains the chemical or physical-chemical state of minerals in the small intestine; therefore elements that remain linked to the molecules and other inorganic complexes, following the completion of the digestive process, will not be absorbed and will be eliminated in the feces.

Minerals may have negative interaction with other minerals potentially affecting intestinal absorption, storage, transportation and biologic use. Iron, because of its high affinity with electronegative atoms like oxygen reacts favorably to form macromolecules. In the Fe^{2+}, state it forms complexes with the hydrogen ion, with water and other anions: such complexes are so big that solubility becomes impossible leading to aggregation with pathological consequences.[9] On the other hand, iron linking to other compounds with lower molecular weight, as sorbitol and fructose, favors absorption.[11,13]

Fernandes *et al.*[24] studying the effect of iron deficiency anemia on dissaccharidase and morphokinetic epithelium of the jejune mucosa conclude that produced lactase was influenced by iron deficiency, with significantly low levels and in fact changes in population and cellular proliferation in the intestinal mucosa were not reported.

Another study suggests the positive effect of alpha-tocoferol on iron bioavailability for milk supplementation.[25] Research focusing on lactoferrin, a milk protein, reveals that it increases iron absorption in the neonatal period contributing with high iron availability in human milk.[26]

Nevertheless other substances antagonize iron absorption according with an experimental study in rats determining that coffee and caffeine reduce serum levels of iron, increase level of transferring and decrease level of ferritin.[27]

Dissociation of iron linked ligands

Cooking food promotes the dissociation of iron linked ligands. Much of the iron contained in natural food is inorganic iron with small absorbing combinations for like other metals, iron forms numerous insoluble salts.[10] Rosa e Trugo[26] postulated that partial degradation of lactoferrin in two fragments resulted in the capacity loss to augment iron uptake through the vilosity of the brush border membrane of the intestine.

Trace elements interaction in Venezuelan diets studied with the introduction of iron and vitamins supplements in farina were analyzed to determined benefits. It was noted that Vitamin A and beta-carotene can form a complex with iron making it soluble in the intestine lumen preventing the inhibiting effects of polyphenol on iron absorption.[22] An experimental research with Caco-2 by Garcia *et al.*[28] determined that beta-carotene overcomes the action of potent iron absorption inhibitors and increases iron uptake. In addition in the presence of phitate and tannic acid generally beta-carotene overcomes the inhibiting effects of both compounds depending on concentration. Siqueira *et al.*[29] findings suggest that bioavailability of Ca^{+2}, Fe^{+2} and Zn^{+2} in a multimix formula offered to malnourished rats was not affected by the phitates it contained.

Pathologic processes in the gastrointestinal tract

Anatomic, physiological and chemical aspects interfere in the form of potentializing or retarding food metabolism in the gastrointestinal tract, changing iron absorption, among them, dyspepsia and gastrointestinal alteration, diarrheas and parasitosis, malabsorption syndrome and infectious processes.

Dyspepsia and gastrointestinal alterations

The degree of gastric acidity intensifies solubility, therefore, the bioavailability of iron in food. The absence of gastric acid secretion (achlorydria) as well as inadequate secretion (hypochloridria) or even the presence of alkaline substances such as anti-acids may interfere in the non-heme iron absorption. Ruhl and Everhart[30] referring to the relation between esophagitis and iron deficiency anemia admitted to the need of further studies, nevertheless, in relation of hiatus hernia they concluded it could be a possible cause for iron deficiency anemia. Naveh *et al.*[31] in experiments with rats determined significant iron absorption reduction due to acetic acid induced intestinal inflammation.

Diarrheas and parasitosis

Diarrheas and parasitosis prevents an adequate iron flow to the enterocytes.[17,32,33] Diarrheas accelerate peristaltic rhythm in addition to being to a great extent associated to helminthes considered the possible cause of damages specially when intestinal infestation is intense. Morbidity promotes mechanical and chemical lesions on the duodenal mucous with occult blood loss through the intestine, which also occurs in ancylostomiasis related to high levels of iron deficiency anemia, significantly so in infested children suggesting that ancylostomiasis has a negative impact on iron status.[33,34]

Malabsorption syndrome

Malabsorption syndrome and precarious fat digestion causing moderate steatorrheas are included as potential situations of iron flow reduction in the intestinal lumen to the intracelular space. Savilahti[35] reports the damage caused in the jejunum following cow milk formula intake for young children who presented moderate steatorrhea, D-xylosis absorption reduction, frequent iron deficiency anemia and hyproteinemia.

Infectious processes

Studies have demonstrated the aggression to the intestinal mucosa causes alterations in iron absorption. Infection by *Heliobacter pylori* (H. pylori) may lead to iron deficiency in children.[36] Other authors[37-39] refer to the association between low levels of serum ferritin and *H. pylori* prevalence. Marignani *et al.*[40] and Konno *et al.*[41] suggest that *H. pillory* infection could be involved in cases of unknown iron deficiency anemias and that the eradication of these bacteria could be associated to the resolution of anemia. Ferripenic anemia was also present in patients with atrophic gastritis and *H. pylori* infection.[42]

Discussion

Classical interventions to deal with the problem of iron deficiency anemia such as: pursuing new nutritional habits, clarification on facilitating and inhibiting iron absorption factors, fighting blood spoliation parasitosis, preventive measures for infectious diseases, food supplementation, as well as medicament supplementation with iron salts have been feeble in facing the high rates of iron deficiency and iron deficiency anemia in Brazil and in the world.

In a study including children of six to 59 months old in Pernambuco, Osório,[4] in 2000, detected that iron food consumption did not reach daily recommendations of 10 mg. the consumption being lower in younger ages and that bioavailable iron present in children's food consumption was low in the majority of age groups in all of the geographic areas. The rural interior reached an average of practically half of the advisable dose (0.49 mg) giving rise to the very high anemia prevalence in the order of 51.4% in the interior against 40.9% for the State.

On the other hand, in a research developed by Cavalcanti *et al.*[5] with the association of ferrous sulfate to Vitamin A given to children in public day-care centers in the city of Recife where anemia prevalence was of 82.4%, the treatment did not produce satisfactory results in fighting the disease. This encouraged Siqueira *et al*.[43] to develop a study to assess the probable coexistence of inhibiting substances that might be interfering in the absorption of iron contained in food/medicament offered to the children. They analyzed theoretical menus and the ones offered to the children and identified low iron content in both of 5.4 mg and 4.8 mg for each 1000 kcal respectively. Such values are lower than the values described in the literature (6 mg for each 1000 kcal). They also detected a great quantity of milk in relation to other components of the menus studies, a percentage of 16% of milk in the total caloric volume for the recommended menu and 17.6% of the menu offered with a resulting increase in calcium content known as an inhibiting substance in iron absorption in addition to the fact that the milk served was not supplemented with iron.[7]

Occult blood losses in the feces have been reported in newborns fed with pasteurized cow milk[18] that may induce absorption deficiency.[35] With preparation and offer preceded by a careful technical and educational orientation, iron absorption efficiency may be improved with diet planning, with the concurrent intake of milk, tea and coffee avoided.[7]

Associated to these factors, that antagonize iron uptake the risks of low breast feeding rates in our environment should be added, according to research of Lima and Osório.[44] The authors determined a mean duration of 199.8 days for breast feeding, with 90.4% of the children being nursed in the first month of life; from four to six months percentages were 64.7% and 54.5% respectively[44] results similar of Spenelli's *et al.*[45] who identified breast feeding prevalence in 97.2% of the children in a mean period of 5.6 months.

When detailing data analysis, the authors determined that of the 80.4% children nursed in the first month of life and at the end of the forth month, 50% had been already weaned. Audi *et al.*[46] noted that exclusive breast feeding was of 64.8% in the first month, falling to 45% to 30.1% from four to six months respectively with the early introduction of tea and other types of milk.

Prenatal care and breast feeding viewed as the support and follow-up of maternal and child quality healthcare should mobilize new strategies to improve the efficacy in treatment and correction of the high anemia prevalence rates in mother and child. As for pre-natal care, Pereira[6] reports that he has not found a statistically significant difference for the condition of anemia (91.7%) and non-anemic (94.3%) among mothers who reported having had prenatal care. Similarly he also determined that anemia prevalence (42,2% com Hb <11 g/dl) among mothers who reported having used iron medication to be similar to the ones who did not. Santos e Batista Filho[47] while studying the condition of anemia in prenatal care in Pernambuco determined that in half of the health clinics there were no technical procedures (diagnosis, prevention and treatment of anemias) and found that to be a crucial constraint to face the problem with desirable efficiency.

It's important to consider other precipitating events in the scenario of iron deficiency anemia resisting treatment with iron salts, using copper deficiency as an example, the absorption of copper is inhibited by fructose and vitamin C that interfere with its uptake and organic interaction with iron.[18] Kolsteren *et al.*[48] study also reports the value of zinc and Vitamin A synergism to iron to correct anemia.
Discussion on iron deficiency anemia, its consequences and intervention measures should be a priority in the background of future healthcare professionals, as well as the need to promote training to personnel working with mothers and children.

Final considerations

Iron absorption *deficit* results in nutritional iron deficiency and iron deficiency anemia in our days recognized as being a worldwide problem, a healthcare issue in developed and developing countries with an important impact on more vulnerable groups such as: children, school-age children, fertile women, pregnant women, women in the puerperal period and nursing mothers.

Because of the value of iron in organic metabolism and the fact that stock balance and iron rigorous recycling by the organism are utmost important to life, in general, in these vulnerable groups, the adequate status of iron is not timely provided. Therefore, studies accomplished in this field of knowledge are valuable because they pursue the clarification of processes favoring or inhibiting iron uptake in the lumen of the digestive tube, and aim at establishing a therapeutic and preventive approach more adequate to fight iron deficiency and the resulting anemia.

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