Interaction of Iron with Other Nutrients

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Iron is essential for oxygen transport, oxidative metabolism, and cellular growth. Interactions between iron and other dietary factors play a significant role in determining the adequacy of iron nutrition and have important implications for food fortification in developing countries. Vitamin A and vitamin C deficiency states may affect iron transport, metabolism, and storage within the body.

Introduction

Iron plays an essential role in many metabolic processes including oxygen transport, oxidative metabolism, and cellular growth. In human beings it is absorbed primarily in the duodenum, transported through the blood stream and extracellular fluid bound to transferrin, and stored intracellularly predominantly in the form of ferritin. Iron balance is rigorously controlled by the regulation of absorption. Physiological iron losses from the body are small.

Both an inadequate supply of iron to body tissues and excessive iron accumulation within the body lead to significant morbidity. Many components of the diet as well as a person's nutritional status with respect to nutrients other than iron can have a significant impact on both iron absorption and internal iron metabolism. The first part of this review will focus on the effects of food composition on iron absorption, and the second on nutrients that affect iron transport, metabolism, and storage within the body.

Iron Absorption

Iron is widely distributed in human food items.[1] Animal tissues contain iron in the form of heme, ferritin, and hemosiderin as well as iron bound to membranes and low-molecular-weight compounds. Iron in other animal-derived foods may also be bound to specific proteins such as lactoferrin in milk, ovotransferrin in egg white, and phosphovitin in egg yolk. Plant foods contain iron in the form of metalloproteins, plant ferritins, iron present in the sap, and iron complexed to structural components or storage compounds predominantly as phytates.[2] In addition, food may contain contaminant inorganic iron salts such as ferric oxides and hydroxides[3] or iron compounds added during processing to fortify the diet.

Over the past 30 years considerable progress has been made in understanding iron absorption by employing radioisotopes of iron for human absorption studies. The isotopes were initially incorporated into the food items being studied by hydroponic methods for vegetable foods and biosynthetic techniques for animal foods. Considerable variation in the absorption of different food items was observed. Iron derived from animal tissue was generally better absorbed than that of vegetable origin.[4] However, when meals containing two foods labeled with separate iron isotopes were studied, the absorption of iron from each was found to be modified by the other. This led to the important discovery that iron bioavailability is determined by overall meal composition and under most circumstances is not a unique property of the food source. As a consequence, the methodology for measuring food iron absorption was simplified considerably since it is possible to label the meal with a trace amount of a radioisotope merely added before consumption, avoiding the necessity for intrinsic tagging of multiple meal components.[5,6] Several further studies refined our current concept of the behavior of iron destined for absorption in the lumen of the upper small bowel prior to its entrance into the mucosal cells.[7–9] Iron behaves as though it is derived from one of two common iron pools in the meal.[10] The larger pool comprises iron in vegetables, any soluble inorganic iron present, and iron in meat that is not in the chemical form of heme (*nonheme iron pool*). Heme compounds, primarily hemoglobin and myoglobin in meat, account for about 10–15% of ingested iron in industrialized countries and constitute a separate pool with a different absorption behavior (*heme iron pool*).

Nonheme Iron Absorption

Iron storage status is the most important determinant of the rate of nonheme iron absorption. However, factors present in the intestinal lumen exert a powerful influence over the body's ability to extract iron from the luminal nonheme iron pool. Two physiological factors—gastric hydrochloric acid secre-

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tion and the retention and mixing of food in the stomach—are necessary for optimal absorption. Gastric acid is important for the solubilization of nonheme iron in food. Bezwoda et al.[11] demonstrated an inverse relationship between the pH of gastric juice and both the solubilization of nonheme iron from a standard meal as well as percentage absorption. Skikne et al.[12] showed that when absorption from Western diets is studied, a marked reduction in gastric acid output is necessary before absorption is measurably reduced. Nevertheless, patients with achlorhydria, particularly those who have had extensive gastric surgery, usually develop iron deficiency anemia due to a diminished ability to absorb nonheme food iron unless they take supplements.[1]

The absorption of nonheme iron is maximal when a soluble iron salt is administered to an iron deficient individual in the fasting state. This is the basis of the reference absorption measurement (ferrous sulfate with ascorbic acid), which has been used by many investigators to adjust for variations in individual iron requirements between different experimental subjects when evaluating the bioavailability of sources of dietary iron.[13,14] In comparison with the reference value, almost all meals significantly reduce the percentage of iron absorbed. However, several dietary factors may act as either enhancers or inhibitors of absorption from the common nonheme iron pool formed in the stomach and the upper small intestine. The balance between these factors determines the bioavailibilty of the nonheme iron in the meal.

Enhancers of Nonheme Iron Absorption

Ascorbic Acid. When ascorbic acid is added to a vegetable meal, percentage absorption is increased in approximate proportion to the molar ratio of ascorbic acid to iron irrespective of whether the ascorbic acid is introduced as the purified compound or in the form of fruits with a high ascorbic acid content.[15] In one study, as little as 20 mg ascorbic acid added to a maize porridge meal fortified with 2 mg or 4 mg iron increased absorption 1.7- and 1.8-fold, respectively.[16] Absorption from vegetable-based meals may be increased as much as sixfold by larger quantities of ascorbic acid (Figure 1).[15] The influence of ascorbic acid is most pronounced in inhibitory meals, and it is effective in meals that contain high levels of the two main inhibitors of nonheme iron absorption, phytates and polyphenols.[17,18] A much smaller promoting effect occurs when it is added to a high bioavailability meat-containing meal.

Ascorbic acid is effective in promoting iron absorption only if eaten together with the iron. Cook and Monsen[17] demonstrated that 500 mg ascorbic acid taken with a meal increased absorption about sixfold, whereas the same quantity had little effect when taken 4 or 8 hours before the meal. Methods of food preparation, especially baking at high temperatures[16] or prolonged rewarming,[19] may lead to oxidation of the vitamin and the loss of its beneficial properties.

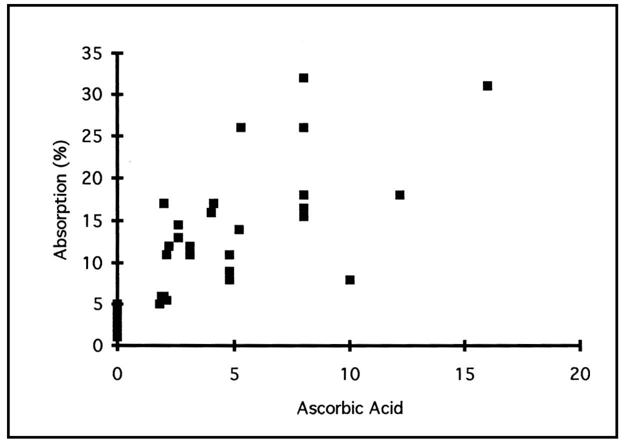

Figure 1. Relationship between mean nonheme iron absorption corrected for reference absorption and molar ratio of ascorbic acid to iron in vegetable meals (redrawn from Lynch and Cook[15] with permission).

Ascorbic acid acts by maintaining iron in a soluble bioavailable form as the luminal pH rises once the gastric contents enter the duodenum. Iron, particularly when it is in the ferric form, is soluble only at acid pH. Ferric iron has a coordinating valence of 6. In aqueous solutions metal ions are bound to each other through water bridges. If the pH rises, hydroxide ions become available and metallic polymers or precipitated metallic hydroxides are formed. Above a pH of 4 almost all the iron is precipitated from a solution of ferric chloride. However, if ascorbic acid is added to soluble ferric chloride in an acid solution, a complex of iron and ascorbic acid is formed that remains soluble over a wide pH range.[20]

Organic Acids. Although less well studied than ascorbic acid, several other organic acids appear to have comparable enhancing effects in single-meal studies. Gillooly and coworkers[21] measured iron absorption from 17 vegetable meals. All the vegetables associated with good iron bioavailability contained appreciable amounts of one or more of the organic acids citric, malic, or ascorbic acids. The addition of citric, malic, or tartaric acids to a rice-based meal improved iron absorption two- to fourfold.[21,22] The high absorption of iron from maize and sorghum beers in sub-Saharan Africa is due to the presence of lactic acid.[23]

Animal Tissues. Several animal tissues, including beef, chicken, fish, lamb, liver, and pork, improve iron status both by supplying highly available heme iron and by improving absorption from the nonheme iron pool.[24,25] Unlike ascorbic acid, there is only a modest rise in percentage absorption with increasing quantities of tissue protein. The factor(s) in animal tissue responsible for these beneficial properties remain poorly characterized. It has been suggested that peptides released during proteolytic digestion by pepsin in the stomach may increase the solubility of inorganic iron.[26–28] Martinez-Torres and Layrisse[29] proposed that the meat effect is a specific property of its amino acid composition and that, in particular, cysteine-containing residues are important.[30]

It is unlikely that the cysteine itself is an important enhancer of iron absorption, but enzymatic digestion of the two major myofibrillary proteins of meat, actin and myosin, produces a large number of cysteine-containing peptides that are stable in the gastrointestinal tract with thiol groups that tend to remain unoxidized.[31] These peptides could bind iron, maintaining its solubility and availability for absorption. However, some in vitro studies have provided contradictory evidence suggesting that iron in the presence of enzymatic digestion products of meat is complexed with carboxyl and not thiol groups.[32,33]

The effects of animal tissue may be more complex; several mechanisms could be involved. Torrance et al.[34] proposed that meat may act primarily by reducing the inhibitory effect of polyphenols. Kapsokefalou and Miller[35] found an increase in stable ferrous iron during in vitro beef digestion, suggesting that meat has a reducing effect. Finally, Zhang et al.[36] proposed that meat may act by stimulating gastric acid production.

Inhibitors of Nonheme Iron Absorption

Phytate. The reduced iron absorption from meals containing wheat bran led Widdowson and McCance[37] to suspect that phytate is an important inhibitory factor. A large number of subsequent studies have demonstrated that phytate is indeed a major inhibitor in cereal foods such as wheat, oats, sorghum, unpolished rice, and beans.[21,38–40] One earlier study failed to demonstrate differences in absorption from meals prepared with soybeans containing widely differing quantities of phytate.[41] Recent careful quantitative measurements have provided an explanation for this finding. Studies using both wheat[42] and soybeans[40] show that even small quantities of phytate are strongly inhibitory (Figure 2). Moreover, in the study reported by Hurrell and colleagues[40] using soybean protein isolates, there was no increase in the inhibitory effect of phytate at phytic acid concentrations above 4 mg per gram of soy protein isolate. This finding has important practical implications. It may be possible to dephytinize food products to improve iron absorption, but it is clear that dephytinization will have to be relatively complete to be effective.

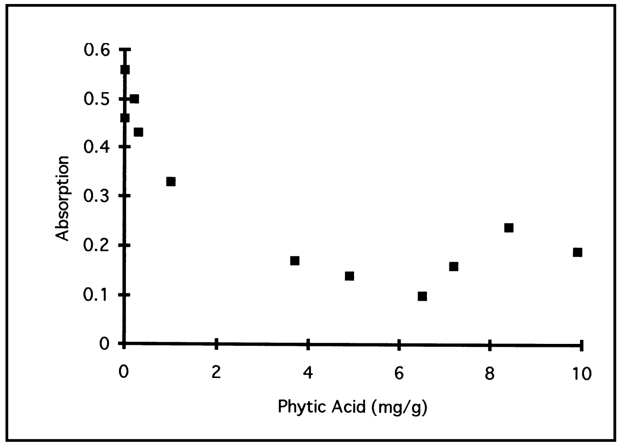

Figure 2. Relationship between nonheme iron absorption and the phytate concentration (mg/g) in 11 meals containing a soy protein isolate. Absorption is expressed as a fraction of the absorption of a control meal containing egg white to eliminate the effect of variation in iron status between experimental subjects. The approximate phytic acid content (mg) per meal can be calculated by multiplying the phytic acid concentration (mg/g) of the soy protein isolates by 33 (redrawn from Hurrell et al.[40] with permission).

The details of the mechanisms by which phytates inhibit iron absorption have not been characterized. Monoferric phytate, which constitutes only a small proportion of the phytate in bran, is not inhibitory,[43] but the formation of diferric and tetraferric phytate complexes in the gastrointestinal tract may render iron unavailable for absorption.[44]

Polyphenols. Tea was found to be a powerful inhibitor of iron absorption by Disler and coworkers.[45] Subsequent studies indicated that this is primarily the result of its tannin content.[46] Polyphenols are present in other popular beverages and are common constituents of many vegetables including several cereals. They appear to be equal in importance to phytates as inhibitors of nonheme iron absorption. The extent of inhibition varies inversely with the condensed polyphenol content.[21] As is the case for phytate, the maximal effect occurs at relatively low polyphenol concentrations (Figure 3). This has been demonstrated both by measuring nonheme iron absorption from meals containing foods with varying polyphenol contents and by evaluating absorption from wheat rolls or dephytinized bread to which increasing quantities of tannic acid were added.[18,47] Polyphenols are thought to act through the formation of complexes between the hydroxyl groups of the phenolic compounds and iron molecules, rendering the iron unavailable for absorption.

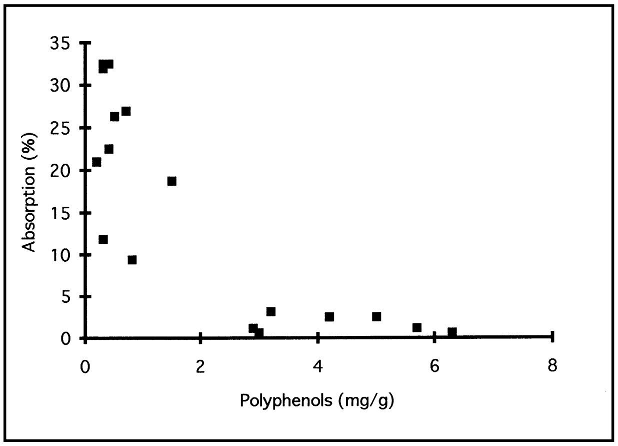

Figure 3. Relationship between condensed polyphenol content of vegetables and mean nonheme iron absorption (redrawn from Gillooly et al.[21] with permission from Cambridge University Press).

Protein Digestion Products. While animal tissues improve nonheme iron absorption, other proteins of both animal and vegetable origin exert an inhibitory effect. When tested in a semipurified meal of hydrolyzed maize starch, corn oil, and a protein source, animal protein foods such as whole milk, casein, and whey proteins derived from milk, cheese, whole egg, and egg white as well as purified bovine serum albumin diminished absorption to between 50% and 10% of the value obtained using a meal comprising only hydrolyzed maize starch and corn oil.[24,25,28,48] Bovine serum albumin was the least inhibitory and whey protein the most. Two vegetable proteins tested (wheat gluten and soy protein) also had a marked inhibitory effect .

Some vegetable foods that are important sources of dietary protein have been studied in greater detail. Several legumes[49,50] and members of the nut family reduce nonheme iron absorption.[51] Processing may be important in the case of soybean foods. A number of widely used products such as full-fat soy flour, textured soy flour, and isolated soy protein are markedly inhibitory.[52–55] On the other hand, fermented foods that are important elements in the diets of several Asian countries, such as silken tofu, sufu, tempeh, natto, and miso, render the iron more bioavailable.[56]

The factors in soy products responsible for inhibiting iron absorption have not been characterized completely, although the importance of phytates has been clearly established.[40] However, even soy protein isolates that are essentially phytate-free are markedly inhibitory. Lynch and coworkers[57] were able to demonstrate the presence of a protein-related moiety in soybean protein isolate that inhibits nonheme iron absorption independently from the effect of phytate. The two major protein fractions in soybeans (7S conglycinin and 11S glycinin) were purified and dephytinized. The essentially phytate-free 7S conglycinin fraction had an inhibitory effect approximately equal to that of phytate, whereas the 11S glycinin fraction was only inhibitory in the presence of phytate. The recent observation of McFarlane et al.[56] and Baynes et al.[58] also suggest an important role for protein. They found that improved iron bioavailability in fermented soy products can be correlated with diminishing size of the predominant polypeptides remaining in a given product after fermentation.

Calcium. The addition of calcium in the form of milk or an inorganic salt to a meal reduces percentage nonheme iron absorption in human beings. However, the effect of calcium is complex and the mechanisms by which it interferes with iron uptake are poorly understood. An early study was based on a simple meal of semipurified ingredients that contained little calcium and had low iron bioavailability.[59] The addition of calcium and phosphate diminished percentage iron absorption while the addition of either alone had no effect. More recently Hallberg et al.[60] demonstrated that doses of calcium chloride (between 40 mg and 600 mg calcium) caused a dose-related reduction (up to 300 mg calcium) in nonheme iron absorption from a meal of wheat rolls containing 10 mg native calcium and 3.8 mg iron. When the calcium was incorporated into the dough before baking, the inhibitory effect was greater and appeared to be correlated with an increase in the phytate content of the wheat rolls. The researchers postulated that calcium inhibited iron absorption by two mechanisms in their experiments. Calcium incorporated into the dough reduced phytate degradation during fermentation and baking. Calcium in the rolls at the time they were consumed reduced iron absorption directly. They also found a small reduction in heme iron absorption after the addition of 165 mg Ca as calcium chloride to a hamburger meal.

Cook and coworkers[61] evaluated the effects of various calcium salts commonly used as supplements on the absorption of dietary nonheme iron and iron supplements. When taken without food, calcium carbonate did not inhibit the absorption of ferrous sulfate at a dose of 600 mg calcium and 18 mg iron. Calcium citrate and calcium phosphate at the same dose reduced absorption by 49% and 62%, respectively. When the supplements were taken with a hamburger meal they were all inhibitory. These researchers also evaluated the effect of calcium carbonate, calcium citrate, and calcium phosphate on absorption from two meals that contained no supplements. One was a high-bioavailability hamburger meal and the other a low-bioavailability meal containing egg, bran flakes, and coffee. The inhibitory effect was significantly greater in the latter meal.

Taken together, the two recent human studies suggest that calcium interferes with iron absorption by interactions that occur in the lumen. They appear to be complex and involve other dietary components. The inhibitory effect depends on the meal type, its normal calcium content, and, in some instances, the inhibition of phytate degradation during preparation. These observations may have particular importance for women taking calcium supplements.

Fiber. Components of fiber bind iron in vitro. However there is little current evidence to suggest an important role for fiber in human studies. Enzymatic dephytinization of bran almost completely removes its inhibitory effect.[62] Several purified fiber components have been tested for their effect on human iron absorption. Cellulose and pectins are not inhibitory. Ispagula and psyllium lead to a mild reduction in absorption.[63]

Heme Iron

Absorption from the smaller heme iron pool in meat- and fish-containing meals is much more effective in human beings than is nonheme iron absorption. As is the case for nonheme iron, absorption is increased in the face of iron deficiency, but the proportional change is much smaller.[1] Heme iron is relatively well absorbed under all circumstances. Moreover, heme iron absorption is relatively independent of meal composition and little affected by the enhancers and inhibitors that alter nonheme absorption, although other food components are necessary to ensure adequate absorption. Pure heme iron administered in the fasting state is poorly absorbed.[64] Isolated soy protein has been reported to improve heme iron absorption in one study,[65] and calcium salts were found to be modestly inhibitory in another.[60]

The Importance of Bioavailability in Complex Diets

There is little doubt that bioavailability is an important determinant of iron absorption, but a word of caution is necessary. All of the data described above are derived from testing single meals. Experimental designs were frequently chosen to optimize the potential enhancing or inhibitory effect of a food factor. In most cases meals were consumed after an overnight fast. This does not mirror the usual dietary practices of most people. Western diets are highly varied, leading to a complex interaction between promoting and inhibiting ligands. A recent study carried out in the United States[66] suggests that single-meal studies may exaggerate the effects of specific food items on iron bioavailability. Cook and his colleagues measured the overall absorption from extrinsically tagged bread rolls eaten with 28 separate meals over a 2-week period. This provided a measure of average dietary nonheme iron absorption during the 2 weeks. Diets designed to improve or impair nonheme iron bioavailability were also tested. In each case comparisons were made with single-meal absorption tests. There was good agreement between percentage absorption based on the 2-week dietary labeling and a typical single meal chosen to represent the individual's customary diet. However, the effect of both enhancers and inhibitors of absorption was greater in the single-meal studies, supporting the contention that the impact of food ligands on bioavailability in Western diets may be accentuated in single-meal studies.

The conclusions drawn from this study are supported by survey data. Meat is the only dietary item that has been shown to correlate consistently with iron storage status.[1] Moreover, Cook and coworkers[67] failed to demonstrate any effect on iron stores after 2 grams of ascorbic acid per day were added to the diets of normal American volunteers over a 2-year period.

There is a need for similar dietary labeling studies to evaluate the importance of factors influencing bioavailability in the less-varied diets commonly consumed in developing countries. The diets of infants and children are particularly important in this regard. Intuitively one would expect greater effects on bioavailability and closer agreement with single-meal results. There is some experimental support for this expectation. One example was reported from Chile.[68] Milk fortified with iron and ascorbic acid had a much greater impact on iron nutrition in infants than did milk fortified with iron alone.

Nutrients with Systemic Effects on Iron Absorption

Vitamin A

A direct correlation between serum retinol and hemoglobin levels in women and children has been observed in several surveys.[69–73] An association with vitamin A deficiency as assessed by conjunctival impression cytology has also been demonstrated.[74] Dietary deficiencies of both vitamin A and iron frequently coexist in developing countries,[75,76] but vitamin A deficiency also affects iron transport and red blood cell production directly. Observations made in human beings and experimental animals have shown that the anemia associated with marginal vitamin A deficiency is characterized by a decrease in the serum iron concentration, total iron-binding capacity, and transferrin saturation, and with increased storage of iron in the liver and spleen.[71,77–79]

In populations with low serum retinol levels, vitamin A supplementation alone may result in increased hemoglobin concentrations.[75,80,81] Mejia and Chew[75] studied 99 children 1–8 years old who were suffering from nutritional anemia in an attempt to distinguish the separate pathogenetic roles of vitamin A and iron. The children were divided into four groups and supplemented for 2 months with vitamin A, iron, vitamin A and iron, or a placebo. Vitamin A supplementation produced a significant elevation in serum retinol levels, as well as an increase in hemoglobin, serum iron, and transferrin saturation, but no change in serum ferritin. Iron alone led to a significant rise in both hemoglobin concentration and serum ferritin. The authors concluded that both vitamin A and iron deficiencies contributed to the anemia in these children. More recently Suharno et al.[72] drew similar conclusions from an investigation involving anemic pregnant women in West Java. Both vitamin A and iron administration resulted in improvement in hemoglobin levels, with a greater effect observed in the group given both nutrients concurrently. A rise in serum ferritin concentrations was observed only in the iron-supplemented groups.

These studies suggest that vitamin A deficiency impairs iron mobilization from stores and has little influence on iron absorption. Measurement of the effects of marginal vitamin A deficiency on iron metabolism, erythropoiesis, and red cell survival in rats supports this conclusion. Iron absorption is unchanged or increased.[77–79,82] Iron concentrations in storage organs are increased, but delivery to the developing erythroid cells appears to be impaired. Shortened red cell life span and suppression of hematopoiesis may be additional factors. The similarity between these findings and anemia commonly associated with inflammatory and neoplastic disorders ("anemia of chronic disease") led Thurnham[83] to speculate that vitamin A may act by suppressing acute-phase reactants.

Ascorbic Acid

As previously discussed, the most important interaction between ascorbic acid and iron from the point of view of nutritional anemia is its effect on bioavailability. This appears to be a direct interaction between ascorbic acid and nonheme iron in the lumen of the upper small bowel, which is not related to the individual's ascorbic acid status. Nevertheless, ascorbic acid has been shown to influence the storage and transport of iron in the body. Scurvy still occurs, although rarely, in human subjects with excessive iron stores in southern Africa.[1] Tissue ascorbic acid stores are reduced in many others who have no clinical evidence of scurvy. The low tissue levels are believed to result from a suboptimal dietary intake of ascorbic acid combined with excessive oxidation of the vitamin in the presence of severe iron overload.

Ascorbic-acid-deficient human subjects have a defect in iron release from reticuloendothelial cells. The administration of ascorbic acid to such individuals produces a rapid rise in the serum iron concentration.[84] Studies using scorbutic guinea pigs have demonstrated that storage iron release from hepatocytes is unimpaired but that reticuloendothelial release is defective.[85,86] The factors responsible are unknown. Recent in vitro observations by Toth and Bridges[87] suggest that ascorbic acid may be important for the modulation of ferritin synthesis and therefore iron storage. The mechanism may involve the regulation of mRNA for ferritin synthesis by the iron-responsive protein.

Competition for Absorption with Other Metals

The absorption of metals close to iron in the periodic table of elements is enhanced in iron-deficient experimental animals.[1] They are cobalt, nickel, manganese, zinc, and cadmium. Lead absorption is also increased in iron-deficient human subjects. The enhanced absorption of manganese and cobalt in iron-deficient rats can be inhibited competitively by iron, and vice versa. This finding suggests that iron and other metals may share in part the same absorptive pathway. With the exception of zinc, there is little evidence to suggest an important effect on micronutrient nutrition in human beings.

Zinc

Some concern has been raised about the potential for adverse effects of food iron supplements on zinc nutrition.[88] However, measurements of zinc absorption suggest that there is less interaction between iron and zinc in humans than in rats. Human subjects with an increased capacity to absorb iron do not absorb more zinc.[89] When iron and zinc salts are administered together in the fasting state, a higher zinc-to-iron ratio is required to demonstrate reduced zinc absorption in humans than in rodents.[88] Using a radioisotopic technique and whole-body counting, Sandstrom and coworkers[90] reported no inhibition of zinc absorption at a molar ratio of iron to zinc of 2.5:1 when both metals were administered in water. Increasing the molar ratio to 25:1 reduced zinc absorption significantly. However, when iron and zinc were administered in the same molar ratio with a meal, no inhibitory effect was observed. Other investigators have made similar observations.[88,89] It therefore appears that any influence that iron may have on zinc absorption is much smaller in the presence of the ligands in food that modify the bioavailability of both metals.[88] Even foods that are highly fortified with iron are unlikely to be prejudicial to zinc nutrition unless the zinc intake is very low or the diet is composed of highly purified components.

Measurements of plasma zinc levels in women taking iron supplements during pregnancy have yielded conflicting results.[88] However, the administration of a daily 30 mg iron supplement to 1-year-old infants had no effect on serum zinc concentrations.[91] Finally, the possibility that zinc supplements may interfere with iron absorption also needs to be considered. Yardick and coworkers[92] reported a modest but statistically significant fall in hematocrit and serum ferritin levels in 18 female volunteers 25 to 40 years old taking a 50 mg per day zinc supplement without additional iron.

Summary and Conclusions

In nutritional anemia the most important interactions between iron and other food components affect the absorption of nonheme iron. Iron deficiency anemia results from the inability of absorptive mechanisms to extract sufficient iron from many foods. Dietary factors may enhance or inhibit iron absorption. The best-characterized enhancers of iron absorption are animal tissues such as meat, poultry, and fish and organic acids. Ascorbic acid has been studied the most extensively, but other organic acids such as citric, malic, tartaric, and lactic acids are also effective. The major known inhibitors of iron absorption are phytates and polyphenols, as well as several animal and vegetable proteins. It is important to note that relatively small concentrations of the most potent and ubiquitous inhibitors, phytates and polyphenols, exert a pronounced effect. Efforts to improve bioavailability would necessitate almost complete removal.

Most studies of iron bioavailability have involved measurements of absorption from single meals. Dietary labeling of a whole Western diet over a 2-week period suggests that the effect of modifiers of bioavailability are exaggerated in single-meal studies. However, this may be a reflection of the complexity of Western diets. There is a need for long-term studies in developing countries.

The interactions of iron with two other nutrients has been studied extensively. Vitamin A deficiency is associated with anemia and reduced circulating iron levels. The anemia appears to be a consequence of impaired iron release from stores resulting in suboptimal iron delivery to the bone marrow. Zinc and iron are both necessary nutritional supplements in many settings. Concern has been expressed that fortification with one may lead to inadequate absorption of the other. While this may occur when solutions of inorganic iron and zinc are administered, there is little support for an important effect when the metals are given with food in the dose ranges considered optimal for fortification.

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