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Iron Absorption, Bioavailability, and Possible Risks of Iron Fortification

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Iron Absorption & Bioavailability

The adult human body contains three to four grams of iron. It is an essential element involved in oxygen transport and storage, cellular oxidative metabolism, cell growth and division and many other biochemical processes. It is also potentially very damaging to cells because it can promote free radical formation. Under physiological circumstances, body iron is efficiently harvested and re-utilized when cells die and total body iron is held within narrow limits. A small amount of iron is lost through the skin, from the gastrointestinal tract, and the urinary tract and as a result of menstrual bleeding. When compared with the total body iron, the quantity of iron lost is very small—approximately 1 mg/day for a man and 1.5 mg/day for a woman.

Iron balance is achieved by adjusting the rate of absorption to meet this loss as well as provide for the requirements for growth in children. Absorbed iron intake requirements are therefore approximately 1 mg/day for men and 1.4 mg/day for women. The total daily requirement for children rises from about 0.5 mg to 0.8 mg during the first decade of life—a proportionately high requirement given their smaller body size and food intake.

In normal human beings, the mucosal cells of the upper gastrointestinal tract adjust the rate of absorption to allow the body to accumulate a little more iron than is needed for its functional requirements. This iron enters the body's iron store. However, the rate of iron absorption is rapidly curtailed as the size of the iron store increases, preventing the accumulation of unnecessary and potentially harmful quantities of iron by the body. The ability of the absorptive mechanisms to prevent the absorption of iron when iron stores are sufficient is extremely important since the human body has no physiological mechanism for increasing the rate of iron excretion. On the other hand, if the requirement for iron is increased (growth, pregnancy, blood loss), the iron store is utilized first—prior to the body's increasing absorption. As the size of the iron store decreases, the rate of absorption rises. Individuals eating a Western diet can increase iron absorption four-to five-fold once all the storage iron has been used.

The ability of the absorptive mechanisms to finely regulate iron absorption, under all but the most extreme circumstances, would ensure strict iron balance if the dietary iron supply was always adequate and present in an easily assimilable form. However, this is not always the case. In reality several other factors play a crucial role. They are:

a. The quantity of iron in the diet. Iron is well distributed among different foods. Food iron intake is therefore related to caloric intake. The iron content of typical Western meals is about 6 mg/1000 calories. Iron intake is several times higher than the iron requirement. In the United States, normal adult men maintain iron balance by absorbing about 6 % of the iron they consume while normal adult women absorb about 15% because of their greater requirements and lower caloric (and therefore iron) intake. Young children also need to absorb 10-15% of the iron they ingest to meet the requirements for growth and expansion of the red cell mass. In some countries iron intake is lower because major staples such as low extraction wheat flour or polished rice, provides less iron. Even in these situations dietary iron intake exceeds daily requirements.

b. The chemical form of the iron. Iron that is insoluble in gastric juice is not absorbed. Soluble food iron exists in one of two forms: heme iron that is derived from hemoglobin and myoglobin in meat (the iron remains as part of the porphyrin complex which is absorbed intact into the mucosal cells), and nonheme iron which is the soluble elemental iron extracted from all other iron containing compounds. The heme iron in meals is always very well absorbed and is a very dependable source of iron for preventing iron deficiency. Heme iron constitutes only a small fraction of the iron even in Western meals. Nevertheless, because of its high bioavailability it makes a significant contribution to the amount of iron absorbed.

c. The composition of the meal. There are two major reasons for the high prevalence of nutritional anemia in developing countries. First, iron requirements may be increased by disorders such as hookworm that cause pathological blood loss. Second, most, if not all of the dietary iron is in the nonheme form. The body has considerable difficulty in extracting nonheme iron from many vegetable and grain diets because certain chemical compounds in food inhibit absorption. Therefore in many developing countries, even though the intake of dietary iron from whole grains is quite high, the amount absorbed is actually quite low.

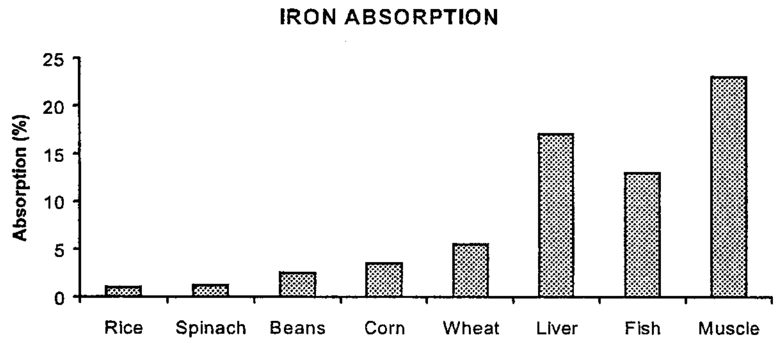

Figure 2a

Measuring Iron Absorption

Our understanding of iron absorption and the modifying role of meal composition was facilitated by the discovery of simple techniques for measuring iron absorption in human beings. (See Figure 2a). Radioisotopes of iron were used in the earlier studies. In both normal and iron deficient individuals, eighty percent or more of any absorbed iron is present in circulating red blood cells two weeks after it is ingested. Therefore, absorption can be measured readily in relatively large numbers of individuals by offering radioactively tagged meals and assaying the radioiron content of a blood sample two weeks later. Similar techniques are now being employed utilizing stable isotopes.

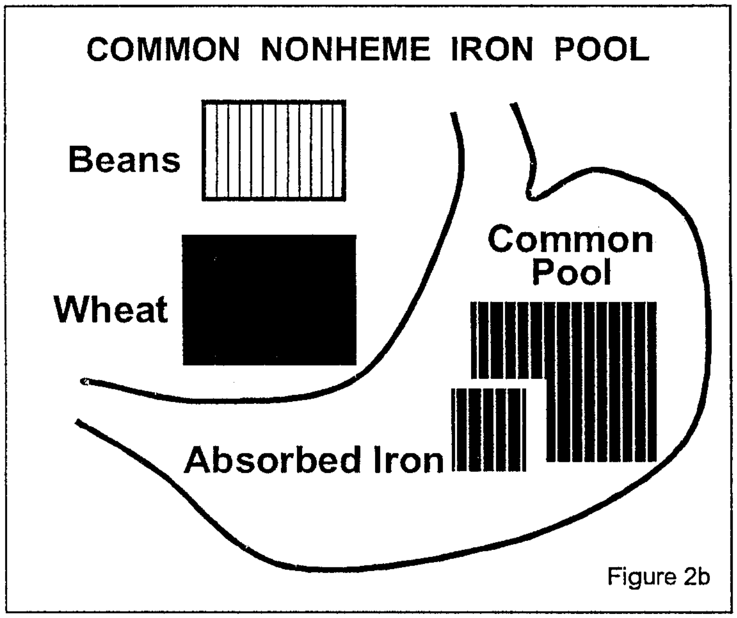

Figure 2b

The early studies of dietary iron absorption were based on foods that were prepared from plants grown in hydroponic culture media containing radioactive iron or animals that had been injected with radioactive iron (intrinsic labeling). The investigators could therefore be reasonably certain that measured absorption was really representative of actual food iron absorption. There was an extraordinary range in terms of the percentage of iron absorbed from different foods. Iron in vegetables and grains was relatively poorly absorbed, ranging from about 1% for rice to 5-6% for wheat. Iron from meat was absorbed much more efficiently, between 10-20%.

It would have been very difficult to measure absorption from every single different kind of food. Fortunately, an important characteristic of nonheme food iron absorption has been discovered. If two foods with markedly different absorption values for iron were labeled with different radioiron isotopes and mixed in the same meal, the absorption of both radioiron isotopes was the same and lay somewhere between the two extremes. Therefore, it became evident that when several foods are eaten together in the same meal, soluble nonheme iron destined for absorption behaves as though it is derived from a single common pool formed in the stomach and duodenum. (See Figure 2b). Absorption from this pool is determined by the combination of factors that affect iron absorption present in the whole meal. Fortification iron enters this pool and is subject to the same influences as the nonheme iron naturally present in the food.

Factors Affecting Absorption

Many of the most important factors affecting iron absorption (bioavailability) in mixed meals have been identified. (See Figure 2c). Absorption is improved by ascorbic acid, other organic acids, and animal tissues. Ascorbic acid has a concentration dependent effect: the more ascorbic acid present, the greater the effect. Animal tissue, on the other hand, improves absorption by a factor of about two only if present in sufficient quantity.

Major inhibitors of absorption are found primarily in vegetable foods and beverages such as tea and coffee. They include phytates, polyphenols and vegetable proteins. Proteins derived from sources other than animal tissues, e.g. milk and egg proteins are also inhibitory. It is important to note that the major inhibitors in vegetable meals, phytates and polyphenols have a very significant effect even in fairly low concentrations.

As a result of the presence of these dietary compounds, typical diets eaten in developing countries consisting primarily of cereals, roots or tubers, and legumes—with negligible quantities of meat, fish and ascorbic acid rich foods—result in low bioavailability (approximately 5%). Diversified diets eaten in Western countries containing generous quantities of meat, poultry, fish and foods containing ascorbic acid are much better sources of iron (approximately 15% average bioavailability).

ENHANCERS AND INHIBITORS OF NONHEME IRON ABSORPTION

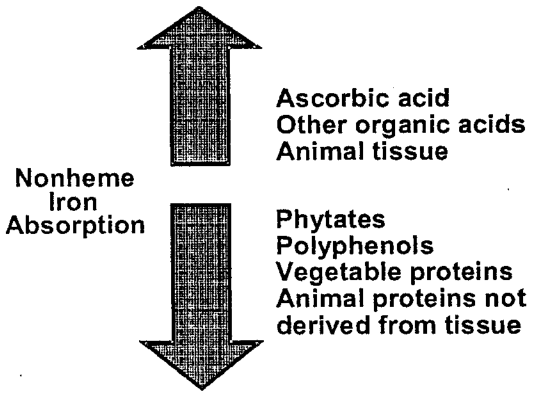

Figure 2c

Iron Fortification:
Selection of Iron Compound for Food Fortification

Fortification is the process of adding nutrients to food to improve the quality of the diet. One justification for fortifying milled cereals is to replace the nutrients lost in the milling process. However, in countries where iron deficiency is highly prevalent, iron fortification is viewed as a means of delivering additional bioavailable iron. Iron fortification of food is considered to be the most efficient and cost-effective method for improving the iron nutrition at a national population-wide level.

There are several technical constraints that limit the addition of any particular iron compound to many foods. They will not be dealt with here. The following discussion will deal only with the importance of using a bioavailable iron compound and of ensuring that adequate bioavailability is maintained in the real meal settings. Although it is possible to fortify food with heme iron, technical difficulties have prevented its implementation outside experimental trials. Fortification therefore entails the use of a bioavailable iron salt or iron chelate.

To be effective, an iron compound must be soluble in human gastric juice. Ferrous sulfate is freely soluble in water and gastric juice. It is the cheapest and most widely used iron salt for food fortification. It is customary to characterize the bioavailability of other iron compounds by comparing their bioavailabilities with ferrous sulfate. Designated relative bioavailability (RBV) is derived from experiments in which the absorption of an iron compound is compared with ferrous sulfate (RBV of ferrous sulfate = 100%). The average RBVs for a few iron compounds that have been considered as iron fortificants are given in Table 1. Results based on human studies are considered to be the more reliable. To be effective, an iron compound chosen for fortification must have an RBV comparable to ferrous sulfate as measured in human studies.

Table 1

Relative Bioavailability of Iron Sources Commonly Used in Food Fortification

Iron Source	Average Human RBV(%)
Iron Salts Freely Soluble in Water	
Ferrous sulfate	100
Ferrous gluconate	89
Ferrous lactate	106
Poorly water soluble	
(soluble in gastric juice)	
Ferrous fumarate	101
Ferrous succinate	123
Elemental Iron	Variable[1]

[1] Depends on particle size, surface area and common nonheme pool acidity in the stomach

Iron Fortification: Bioavailability of Fortification Iron from Meals

The selection of an iron compound that has an adequate RBV as well as the appropriate chemical properties to allow for its incorporation in the target food vehicle is only the first step in designing an effective food fortification strategy. As described above, fortification iron enters the common nonheme pool. Even an iron salt that is freely absorbed when taken without food may be ineffective when added to certain meals. Inhibitors in the meals may prevent all but a small fraction of iron from being absorbed. It is therefore essential to evaluate the bioavailability of the potential fortificant in the context of the meals in which it is to be consumed.

The bioavailability of iron added to meals has usually been estimated on the basis of radio or stable isotope studies in human volunteers. As indicated above, the absorption of iron in these individuals will vary depending on their physiological absorptive capacity, which is in turn dependent on the size of their iron stores. An individual with adequate iron stores will absorb relatively little iron even if highly bioavailable iron is supplied because the absorptive mechanisms are regulated downward.

When measuring iron absorption, the effect of differences in iron status among different subjects must be accounted for since this is a major determinant. This can be accomplished by measuring the absorption from a standard dose of a highly bioavailable iron salt (ferrous sulfate given with ascorbic acid) given after an overnight fast. A standardized bioavailability measurement can then be obtained by making a correction based on the reference dose absorption. Customarily, absorption values are calculated for a reference dose absorption of 40% which was found to be the approximate value obtained in most individuals with absent iron stores, but not anemia.

A large body of experimental evidence obtained over many years indicates that the mere addition of iron to common foods in developing countries is unlikely to have significant impact on iron status. In addition to adding dietary iron, it will be necessary to improve the bioavailability of the iron. From a theoretical point of view, this can be done in a number of ways. Bioavailability can be improved by removing inhibitors from the diet. This could involve a combination of dietary education to reduce the intake of tea or coffee with meals as well as technological approaches to lowering the levels of these substances in foods. However, it will be necessary to reduce the concentrations of the important inhibitors, phytates and polyphenols, to very low levels.

Additional animal tissue in the diet would be a very effective approach. This is not a pragmatically feasible solution because of the cost and, in some cases, the dietary practices and religious beliefs of the people at risk. Alternatively, enhancers could be added. Ascorbic acid is a very attractive option. Bioavailability is improved over a wide range of values depending on the molar ratio of ascorbic acid to iron in the meal. It has been very effective as an additive in infant formulas in Western countries. However, it is relatively expensive and unstable if submitted to prolonged storage in unsealed containers or used in foods that need to be cooked. For a number of reasons, the options outlined above may not be currently realistic to improve population-wide iron status in developing countries.

The search for alternative ways of improving bioavailability continues. Recently there has been considerable interest in ethylenediaminetetraacetic acid (EDTA). EDTA can be added to many foods in small quantities either as sodium iron EDTA or sodium EDTA. It has a major advantage over ascorbic acid in that it is stable during storage and cooking. EDTA interacts with the common nonheme iron pool, releasing iron from inhibitors such as phytates and making it available for absorption. The EDTA itself is only absorbed to a very small extent. However unlike ascorbic acid, the improvement in absorption is limited to a two-to three-fold increase. Moreover, the range of effective molar ratio (approximately 1:1, EDTA; Fe, a little less) is narrow and is critical to ensuring effective enhancement of iron absorption.

Possible Risks Associated with Universal Iron Fortification in Western Countries

The prevalence of iron deficiency has fallen dramatically in Western countries over the last few decades. There is little doubt that iron fortification of foods has played a significant role in this important achievement, particularly with respect to infants and young children. Every effort should be made to achieve similar improvements in the nutrition of individuals in the developing countries. However, an awareness of possible risks of a high iron intake by individuals whose iron requirements are low (men and postmenopausal women) has been stimulated in the United States in recent years by three sets of observations.

a. The demonstration that mean serum ferritin concentrations appear to have increased significantly in the years between the last two National Health and Nutrition Surveys (NHANES II, 1976-1980, and NHANES III, 1988-1994) in all groups of individuals.
b. The observation that, in a carefully conducted epidemiological study carried out in Finland, there was a relationship between high serum ferritin values and the risk for ischemic heart disease.
c. The discovery of a point mutation in the HFE gene (C282Y) that is very common among people of Celtic descent living in Europe, the United States, Australia and South Africa who have hemochromatosis. Over 90% of individuals with phenotypic hereditary hemochromatosis in these population groups are homozygous for this mutation. Recent studies have demonstrated that the homozygous state for this abnormal autosomal recessive gene occurs in at least 1 in 300 individuals with a 1 in 20 heterozygous carrier state. Currently, it appears to be very rare in other ethnic groups studied. Homozygotes are at risk for developing clinical hemochromatosis which is a life threatening clinical disorder characterized by cirrhosis of the liver, primary liver cancer, heart failure, diabetes, damage to other endocrine organs (particularly the pituitary gland), arthritis and skin pigmentation. Heterozygotes accumulate iron stores that are somewhat higher than age-and gender-matched unaffected members of the same population, but do not suffer any harmful consequences.

There is currently no convincing evidence that demonstrates a clear relationship between modestly increased iron stores and clinical disease. Attempts by others to confirm the putative relationship between the size of iron stores (based of serum ferritin concentrations) observed in Finland have yielded conflicting results.

The reasons for the observed increase in serum ferritin concentrations in the HANES III remain uncertain. Factors other than storage iron status may play a role in determining serum ferritin concentrations. It is nevertheless possible that this finding does indeed indicate increasing storage iron status in American men and postmenopausal women. If the latter proves to be the case, it will be very important to discover the reasons and to reverse any trend in this direction. There is no known benefit of having increased iron stores.

One recently reported study, "The Framingham Heart Study," does provide some helpful preliminary information. Ferritin values were higher in men than in women, but did not show an increase with age in these elderly individuals which suggests that there was no progressive rise in iron stores. There was a direct correlation between serum ferritin values and the intake of heme iron, dietary ascorbic acid and iron supplements. Higher ferritin values were also positively correlated with alcohol intake and negatively with coffee consumption. This study demonstrates the potential complexities in dealing with the higher ferritin values recorded in HANES III.

The relationship between dietary iron intake (both quantity and chemical form) and the phenotypic expression of genotypic hereditary hemochromatosis will be the subject of careful study in the coming years since it is now possible to identify individuals carrying one or both mutated genes for the disorder. However, at the present time there is no reason to believe that food fortification with iron significantly affects the size of iron stores in heterozygous individuals. Dietary manipulation has not been shown to play a useful role in the management of the clinical disorder which is customarily treated by the removal of iron by repeated phlebotomy. The current emphasis in dealing with this eminently treatable condition is on early detection and the institution of a program of regular phlebotomies to remove the excess iron and prevent further iron accumulation.

Summary

The cost-effectiveness and the scientific basis of implementing iron fortification is well established. Nevertheless, further research in a few areas remains an urgent necessity. The most important of these is the search for optimal methods for improving food iron bioavailability. The efforts of nutritionists involved in eradicating nutritional iron deficiency anemia should focus on the implementation of fortification programs that are based on the available scientific information relating to iron absorption and iron bioavailability. Concerns about the possible effects of iron fortification on the prevalence and severity of iron overload in vulnerable groups in Western societies should not delay the implementation of fortification in developing countries.