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Iron deficiency and the developing world

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SUMMARY. The dietary intake of iron in underdeveloped countries is based mainly on non-hem iron which is absorbed to a lesser degree that hem iron and is subjected to many interferences from inhibitors generally present in the diets, such as phenols, phytates, fibers, etc.
Food fortification with iron is considered to be the best and cheapest long-term approach for correcting the deficiency. The iron source selected for this purpose has to be soluble, and of high bioavailability, even in a diet rich in inhibitors. Ferrochel may prove to be this type of compound.
Key words: Iron deficiency, anemia, fortification, Ferrochel.

RESUMEN. Deficiencia de hierro y el mundo en desarrollo. La ingesta dietética de hierro en el mundo en desarrollo se basa esencialmente en hierro no hemínico el cual se absorbe en menor grado que el hierro del heme y está sujeto a interferencia por componentes normales de las dietas tales como fenoles, fitatos, fibra, etc.
La fortificación de alimentos con hierro se considera como el mejor enfoque a largo plazo para corregir la deficiencia. La fuente de hierro seleccionada para este objeto debe ser soluble y mostrar alta biodisponibilidad aún en dietas de alto contenido de inhibidores. Es posible que Ferrochel demuestre ser este tipo de compuesto.
Palabras clave: Deficiencia de hierro, anemia, fortificación, Ferrochel.

INTRODUCTION

Iron deficiency is the most commonly encountered nutritional deficiency in humans. More than half a billion people have iron deficiency anemia (1), and many more have depleted iron stores and are at risk for the development of anemia. Paradoxically, iron is the second most common metal in the earth's crust and is present in all foods. Furthermore, the prevalence of iron deficiency anemia varies widely (2). Over the years there has been a steady drop in the prevalence of iron deficiency in industrialized countries, with less than 3% of fertile women in the United States being affected (3). In contrast, iron deficiency is a major problem in the developing world and affects almost all segments of the population including men (4). It is particularly severe in infants and childbearing age women. For example, the prevalence of iron deficiency anemia in preschool children has been reported to be 70% in the Caribbean (5) and between 45 and 70% in Ecuador (6). In pregnant women in West Africa the prevalence ranges between 20 and 45% (2). To comprehend why iron deficiency is so common in the developing world in the face of a plentiful supply of iron and to appreciate the dilemmas that beset iron fortification, it is necessary to have an understanding of basic iron metabolism and particularly the factors that influence the absorption of iron from the diet.

Basic iron metabolism

Iron owes its importance in biology to its remarkable reactivity. The reversible one electron oxidation-reduction reaction between ferrous (Fe (II)) and ferric forms (Fe (III)) is exploited by most iron-dependent enzyme and transport systems and is managed by highly specialized proteins involved in the storage and transport of iron. However, it is this reactivity that produces unacceptable organoleptic changes in food, making the fortification of food with iron difficult. Normally iron can only enter the body through the diet. Four phases of iron absorption are recognized. In the *luminal* phase, food iron is solubilized, largely by acid secreted by the stomach, and is presented to the duodenum and upper jejunum where most iron absorption takes place. Factors which maintain the solubility of iron in the face of rising pH, such as valency (ferrous iron is better absorbed), mucin secreted by the mucosa and chelators (ascorbic acid), appear to be important in this phase. It is in this phase that the presence, or absence, in the diet of promoters and inhibitors of iron absorption is of great importance. In the second phase, *mucosal uptake*, iron is bound to the brush border and transported into the mucosal cell. In the third *intracellular phase*, iron is either stored in cellular ferritin or is transported directly to the opposite side of the mucosal cell and released. In the last phase iron is *released* from the mucosal cell into the portal circulation where it is bound to the transport protein, transferrin. Both iron uptake and release by the mucosal cell appear to be inversely related to the amount of iron stored in the body. Most of the absorbed iron is transported directly to the bone marrow where it is incorporated

into hemoglobin in the red cell. At the end of its life span the red cell is engulfed by cells of the reticuloendothelial system (RES), located mainly in the liver and spleen. The iron is separated from hem and either stored in ferritin or as hemosiderin, both in the RES and in hepatocytes, or released back into the circulation where it is again picked up by transferrin. It should be noted that this cycle is never reversed. There is normally only one way in and there is no way out except through blood loss or, in pregnancy, to the fetus. In reality, a small amount of iron is lost. In men this amounts to about 1 mg/day mainly through loss of blood and surface cells of the gut, urinary tract and skin. The loss is relatively easily balanced by iron absorption. In women, additional losses through menstruation (0.5 mg Fe/day) and the cost of pregnancy (2 mg Fe/day) and lactation (0.5 mg Fe/day) make it more difficult to balance the loss through iron absorption.

Iron balance

Iron requirements must be balanced by iron supply if iron deficiency is to be avoided. Several factors combine to influence iron balance (Table 1). Obligatory iron losses, the requirements of growth and pregnancy as well as pathological losses such as that due to hookworm infection (7) must be balanced against iron supply. Iron supply is heavily influenced by the amount and type of iron in food and the combination of various inhibitors and promoters of iron bioavailability. The major reason for the variation in the prevalence of iron deficiency is to be found in the bioavailability of iron in the staple diets consumed in different regions of the world. Subjects in many developing countrys subsist largely on cereals (8). The iron in which is of low bioavailability because of the presence of inhibitors such as phytates and polyphenols (8). On the other hand, mixed diets of high bioavailability are consumed in Western countries. They contain hem iron, which is well absorbed, together with ascorbic acid and meat, both of which are potent enhancers of non-hem iron absorption (9,10). In essence the problem is one of supply and demand. In regions dependent on cereals the supply of absorbable iron in the diet is limited and may not be sufficient to meet physiological requirements, especially when they are increased by growth, menstruation and pregnancy. While iron balance can also be disturbed at times of increased demand in subjects eating Western diets, the problem is usually a less serious one. Infants are, however, at risk in all populations, since the demand for iron is high and the bioavailability of iron in the infant diet is low (11). Figure 1 shows the changing median iron requirements of males and females with age (12). The upper dashed line represents the amount of iron supplied by a Westernized diet while the lower dashed line represents the iron supplied by a cereal diet typical of the developing world. Neither diet is able to meet the demands of infancy and pregnancy. In women, even the highly bioavailable Western diet is not able to meet the demands of more than 50% of women at menarche, while the cereal diet can not match the requirements of most adult women and some men.

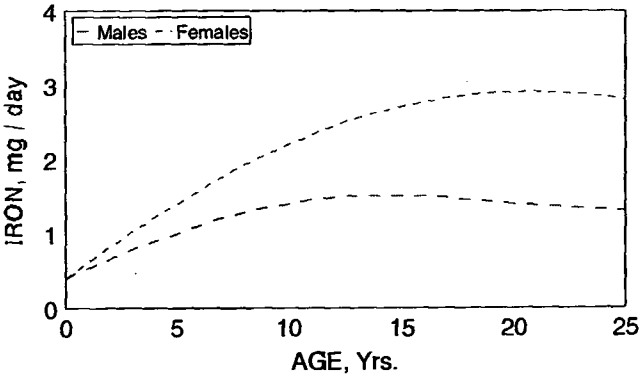
TABLE 1
Iron balance in the body

Iron requirements	Iron supply
Iron losses	**Food iron content**
Menstruation	**Type of iron**
Bleeding	
Hookworm	hem iron
	non-hem iron
	Iron requirements
Iron absorption	
Growtrh	
Pregnancy	Innbhibitors
Lactation	Promoters

Absorption of dietary iron

Fortification of basic foodstuffs with iron is considered to be the best and cheapest long term approach for correcting iron deficiency (13,14) particularly where low iron intake or bioavailability is the primary cause (15,16). However, the fortification of food with iron is not a simple matter and it is worthwhile reviewing the factors involved in the luminal phase of dietary iron absorption since they affect the methods that can be used for fortification.

FIGURE 1
Median iron requirements by age and sex



Common pools in iron absorption

In developing countries the single most important cause of iron deficiency is the low bioavailability of iron in major staple foodstuffs such as cereals and legumes (8). Unfortu-

nately any fortification iron added to such a diet enters the "common pool" of non-hem food iron and, in consequence, is absorbed as poorly as the native iron in the diet. This is due to the fact that the added iron is exposed to the same influences, both inhibitory and enhancing, that influence the absorption of non-hem iron in the diet. Hem iron, which is derived from hemoglobin and muscle, forms a separate pool in the lumen of the gut and is not subjected to inhibitory dietary factors, it is thus far more bioavailable (Reviewed by Layrisse and García-Casal (17)).

Enhancers and inhibitors of iron absorption

The two most important enhancers of dietary non-hem iron absorption are meat and ascorbic acid (9), Hem iron, derived from bovine hemoglobin, has been used successfully to fortify cereals (18,19). The two most important dietary inhibitors of iron absorption are phytates (20) and polyphenols (21). Phytates are widely present in foods and are found in particularly high concentrations in bran (22). Polyphenols are not only responsible for the marked inhibitory effect of tea on iron absorption (23) but are present in a number of vegetables, including sorghum and legumes. They are responsible, in a dose dependent manner, for the poor bioavailability of the non-hem iron present in these foodstuffs (21,24). Polyphenols are also responsible for the marked color changes that may develop in foods fortified with iron (21).

Food fortification strategy

The strategy that should be followed in establishing an iron fortification program has been carefully defined (13,14) (Table 2). It is perhaps significant that those fortification programs and trials that have had only limited success have usually disregarded one or more of the steps. Perhaps the most difficult step in iron fortification is to find a combination of iron compound and food vehicle in which the two are compatible (Step 2). The attributes of the ideal food vehicle are listed in Table 3 (14). The recommended criteria are particularly difficult to meet in developing countries, since the production of staple foods is rarely centralized. The choice of an iron compound presents additional problems. For example a simple iron salt such as ferrous sulfate, is both cheap and bioavailable but its high solubility may lead to the production of colored compounds in fortified food. On the other hand, compounds like ferric orthophosphate which are more stable and therefore do not adversely affect food, are poorly bioavailable (25,26). It follows that it is essential that the bioavailability of the iron compound be assessed in the setting in which it is to be used (Step 4). Both radioisotopic absorption studies prior to a trial and measurement of iron status before and after a controlled pilot trial are useful ways of assessing this. Ferrous iron bis-glycine chelate has potentially great advantages. Unlike other non physiological chelates, one atom of iron is chelated to two molecule of glycine forming coordinated covalent bonds and originating two heterocyclic rings in which the iron atom is central. Glycine is a natural constituent of most foods and is easily metabolized. This compound is already in widespread use as an iron fortificant (27) and is the subject of the articles that follow.

TABLE 2
Steps in developing an iron fortification strategy

1. Determine the iron status of the population
2. Choose an appropriate iron compound and food vehicle combination
3. Establish the acceptability and stability of the fortified vehicle
4. Assess the bioavailability of iron from the vehicle in the appropriate dietary setting
5. Carry out controlled field trials
6. Implement a regional or national fortification program

Effect of iron deficiency on human development

While no one will deny that severe anemia is deleterious to health, there continues to be a considerable debate around the question of weather iron deficiency alone or mild iron deficiency anemia are bad for you. This controversy has been highlighted in recent years by highly publicized claims, unsubstantiated in subsequent work (28,29), of the ill effects of minimally raised iron stores on the generation of atherosclerosis (30) and the prevalence of cancer (31). Apart from ill health endangered by severe anemia, recent reviews have highlighted three areas in which iron deficiency is thought to play an important role. These are pregnancy (27), infection (32) and psychomotor development (33).

TABLE 3
Considerations in the choice of a food vehicle

Consumption	Technical
High proportion of population	Centrally processed
Minimal regional variation	Few production facilities
Unrelated to socioeconomic status	Minimal segregation of fortificant
Minimal individual variation	Good masking qualities
Low potential for excess intake	Low cost
Contained in all meals	Limited stoirage
Linked to caloric intake	High bioavailability

Much of the evidence that iron deficiency is detrimental to the health of pregnant women or to the developing fetus is circumstantial, and well-designed, controlled studies to support the evidence are lacking (27). Equally, there is little evidence to support strongly held views, emanating from the developing world, that supplementation with iron dur-

ing pregnancy is unnecessary or harmful (34,35). The major problems associated with anemia in pregnancy include increased perinatal mortality and morbidity (36), low births weight (37,38), prematurity (39) and the development of iron deficiency during infancy (40). While neonates born to iron deficient mothers appear to have sufficient iron, there is evidence that their iron stores may be reduced (41,42) and that anemia is more likely to develop during infancy (43,40). This has particular relevance when the effects of iron deficiency anemia on psychomotor development are considered. The demands of pregnancy on iron supply are such that women entering a pregnancy with low iron stores will become anemic (44) and there is little doubt that supplementation in these women is necessary. In developing countries, where the background prevalence of iron deficiency is high, routine supplementation would appear to be essential. The impact of iron fortification programs on the outcome of pregnancy has yet to be studied. Indirect evidence that an improvement in general iron nutrition is likely to have a positive effect can be gleaned from the fact that physicians in the iron replete developed world think that iron supplementation in pregnancy is unnecessary (34).

Infants between the age of six months and two years, in both industrialized and the developing world, are at risk for the development of iron deficiency anemia. This is a period of rapid brain growth and the development of cognitive and motor skills. Two important case-control studies have show impairment in psychomotor skills in infants with iron deficiency anemia during this period (45,46). In addition, electrophysiological measurements, performed on iron deficient and non-iron deficient infants, suggest that neurological development is delayed in anemic infants (47,48). Studies showing scholastic performance in school-going children with iron deficiency anemia indicate that this problem continues beyond infancy (49). A worrisome finding in these studies is the lack of improvement in scores on reversal of the anemia although in another psychomotor study, where more prolonged iron supplementation was given, some improvement was demonstrated (50). Although beset by problems of methodology and interpretation, these studies indicate that preventive measures, in the form of adequate iron fortification programs targeted to infants and young children, could play a vital role in improving psychomotor development with long range benefits to the developing world.

In conclusion, iron deficiency appears to be an important factor in retarding the realization of the full potential of people. The key to the improvement of iron nutrition is the development of well- designed iron fortification programs targeted to high risk groups. The development of an iron compound that is bioavailable in the face of a diet rich in inhibitors of iron absorption and with minimal organoleptic problems, is central to achieving this goal. The possibility that ferrous bis-glycine chelate may fill this role deservers further intense investigation.

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