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Iron Deficiency

Causes, Consequences, and Strategies to Overcome This Nutritional Problem

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ABSTRACT

Iron deficiency and anemia affect a substantial portion of the world's population, provoking severe health problems to the people suffering these conditions, as well as important economic losses to the regions in which this nutritional deficiency is significant. In this work, the principal causes and consequences produced by this deficiency are discussed, as well as the different strategies that can be applied in order to prevent and solve this nutritional problem.

Index Entries: Iron; anemia; fortification; supplementation; food.

INTRODUCTION

Anemia and iron deficiency are the most frequent nutritional problems on a worldwide scale, affecting approx 2 billion people, 85% of whom suffer it as a consequence of deficient iron ingestion or the ingestion of an adequate amount of iron but having a low absorption *(1).* Thus, it can be estimated that, at present, 34% of the world's population suffers from iron deficiency, 80% of whom live in developing countries, in which the incidence of anemia and iron deficiency is approx 40%, whereas in developed countries, its prevalence is lower than 10% *(2–5).*

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RISK GROUPS

The principal risk groups (i.e., those having the highest probability of suffering iron deficiency) correspond to those population sectors that have an inadequate iron consumption and/or assimilation together with an increased iron demand. These groups correspond to children, adolescents, pregnant women, and women of reproductive age *(4).*

In the case of infants feeding on milk, the highest prevalence of iron deficiency can be observed between 4 mo and 1–3 yr. During this period, there is a high growth rate, as a consequence of which a high iron demand exists, which should mainly be supplied by the organic stores of this mineral, because the diet is often composed of an excessive consumption of cow's milk, which does not contribute a sufficient amount of bioavailable iron. For instance, in the case of Argentina, it has been demonstrated that as a consequence of the utilization of cow's milk, which has not been fortified with iron, as the principal food for children between 9 and 24 mo, a prevalence of nearly 50% of anemia could be observed *(6).* In any case, the iron deficiency in this group of the population is principally a consequence of diets with scarce absorbable iron, a situation that, in general terms, is associated to the socioeconomic situation of the region *(4).*

During the period of adolescence, iron deficiency is the result of the high growth rate that takes place during this stage of life; adolescents aged between 12 and 15 yr usually increase their weight from 9 to 10 kg/yr. During this period of rapid growth, new biomolecules containing iron, mainly hemoglobin, are synthesized, which consequently determines an increase of the iron requirements. In the case of girls, the beginning of menstruation increases the iron requirements even more, and, consequently, the risk of suffering iron deficiency will be even higher *(4).*

The principal reason that predisposes the group of fertile women to suffer from iron deficiency is the excessive blood loss during menstruation. The use of different contraceptive methods is a coadjuvant factor, which may increase the prevalence of iron deficiency in this group of the population, because the use of intrauterine devices may increase blood losses up to 50% and, consequently, those of iron. However, the utilization of oral contraceptives significantly decreases menstrual blood losses *(4).*

During pregnancy, a significant increase of iron requirements is observed. This is a consequence of the rapid growth of the placenta and the fetus and the expansion of the globular mass, which determines that the total iron requirements during pregnancy are approx 1 g. These increased requirements are usually compensated in part by the iron from the organic store of the metal, which normally, in the case of women, is about 300 mg; the remainder, some 700–900 mg, is compensated for by an increased absorption of dietary iron. The iron stores after childbirth are, therefore, practically exhausted; this situation is an additional risk factor for this group of the population, especially in the case of a consecutive pregnancy *(4).*

However, postmenopausal women as well as men are not real risk groups, because they have no extraordinary increased iron requirements; for this reason, iron in a normal diet is usually sufficient for them to cover their physiological requirements of the metal *(4).*

CAUSES OF IRON DEFICIENCY

It is paradoxical that, although iron is one of the most abundant elements on the planet, its deficiency represents one of the most prevalent nutritional problems. The explanation for this is that most of the ingested iron in food has low solubility and, consequently, low bioavailability.

The change of alimentary habits, which has taken place recently, should also be considered. In order to decrease the caloric intake to preclude obesity, it is probable that this decrease of energy intake determines concomitantly a decrease of dietary iron intake, which may cause anemia in some of the risk groups *(4).*

The most important reason for nutritional iron deficiency and consequent ferropenic anemia is an insufficient incorporation of iron into the organism according to its physiological requirements *(4).*

The principal factors that determine adequate iron incorporation into the organism are the total amount ingested with the diet, the proportion of hemic and nonhemic iron in this diet, the presence of activators or inhibitors of nonhemic iron absorption contained in the food, and the individual nutritional status for this element *(7).*

Furthermore, these factors depend on the physiological status of each person, the cultural habits, and the socioeconomic situation of the region. Thus, for example, the inhabitants of developing countries, because of their unfavorable socioeconomic situation, consume an insufficient quantity of food containing iron; it may also be that the consumed amount is adequate but that the iron contained in the diet is fundamentally nonhemic—that the diet has a low content of ascorbic acid and/or meat and a high content of phytates, tannins, and other inhibitors of the nonhemic iron absorption that decrease the iron assimilation from the food. On the other hand, the population of developed countries generally consumes adequate amounts of food containing fundamentally hemic iron and a high ratio of activators/inhibitors of the nonhemic iron absorption. Therefore, nutritional iron deficiency has a higher incidence in developing than in developed countries *(7–11).*

These causal factors for iron deficiency are a conclusion of a study performed in 1988 by a committee of experts from FAO and WHO. The diets on the planet were divided into three categories, according to the low, intermediate, and high bioavailability of the iron contained in them. The respective absorption percentages for a mixture of hemic and nonhemic iron is approx 5%, 10%, and 15% for individuals with no iron stores but with normal iron transport reserves *(7,12).*

Thus, for example, taking into account the amount of stimulants and inhibitors of iron absorption contained in the meals, a diet of low bioavailability is mainly composed of cereals, legumes, and tubers, which supply a high quantity of phytates; moreover, usually the meat and ascorbic acid content of the diet are less than 50 g and 30 mg per meal, respectively. In individuals with iron deficiency, the total iron absorption is less than 1 mg per day even if the iron intake is higher than 15 mg per day. This low assimilation of the iron contained in the diet explains the high proportion of anemia observed even in sectors of the population considered to be low-risk groups. Low-socioeconomic-level populations of Africa, Asia, and some regions of Latin America consume this type of diet *(7,12).*

A diet with intermediate iron bioavailability is composed of a high quantity of cereals, tubers, and legumes; therefore, these diets have a high phytate content, but, differing from the former case, the meat and ascorbic acid intake is higher than 50 g and 30 mg per meal, respectively. In this case, the absorption of nonhemic iron is approx 8%, which determines that absorption of the total iron contained in the food is between 1.2 and 1.7 mg per day. Consequently, anemia resulting from iron deficiency is restricted principally to those sectors of the population considered as risk groups. Low-socioeconomic-status populations of some Latin American regions consume this type of diet *(7,12).*

The diets of high bioavailability contain a low amount of iron-absorption inhibitors and generous quantities of meat, more than 100 g, and ascorbic acid, more than 50 mg per meal. In this case, the nonhemic iron absorption is enhanced to nearly 15%, which determines that the total absorption of the iron contained in the food is higher than 1.8 mg per day. In this situation, anemia resulting from iron deficiency is restricted fundamentally to the risk groups of the populations but in a lower proportion. The populations of Latin America having intermediate and high socioeconomic levels and the populations of developed regions consume this type of diet *(7,12).*

The situation in developing countries is frequently worse, as a consequence of the high rate of infestation with *Ucinariae,* such as the hookworm, among others. Thus, for example, the rate of prevalence varies between 10% and 20% in dry zones but may be as high as 80% in warm and humid regions, especially if there are poor environmental health conditions *(13,14).*

These parasites produce iron losses resulting from blood losses at the intestinal level, because they adhere to the mucous membrane of the small intestine, ingesting tissue and blood. Different studies demonstrated that the magnitude of blood loss and, consequently, that of iron is correlated to the number of parasites. These losses usually are important because individuals with an intermediate number of parasites loose a blood amount equivalent to 1.2–2.3 mg of iron per day. This high iron loss produces an incidence of anemia up to 41% in the risk groups of the population of those regions in which a high prevalence of infestation exist *(14).*

CONSEQUENCES OF IRON DEFICIENCY

Iron integrates many biomolecules with different biochemical and physiological functions. Its deficiency produces several functional disorders, which generally are increased as the depletion of the essential molecules containing this metal takes place. Many of the clinical symptoms are a consequence of anemia; however, other problems may be the result of a decrease of iron in different tissues or they may be a combination of both processes *(4).*

The principal alterations related to iron deficiency are described below.

Physical Activity, Fitness and Working Capability

The relationship between iron status and the capability to perform a given physical activity was studied in animal models and human beings. The experimental results demonstrate that iron deficiency, in addition to inducing anemia, provokes significant modifications of the muscle metabolism as a consequence of which the capability to perform an exercise or a long physical work is decreased, probably owing to modifications produced at the level of the utilization of glucose as an energy source *(15–17).*

In men, this decrease of the capability to work may imply a loss of productivity, especially in developing countries, where the incidence of iron deficiency is important and the productive activity is strongly dependent on the physical work of the population. Research performed in Indonesia and Sri Lanka demonstrated a decreased working capability of workers with anemia, with regard to those with normal hemoglobin values. It has also been observed that the iron supply not only decreases the prevalence of anemia but also increases their capability to work. It was shown, for example, that in people with moderate anemia, an increase of 10% of the hemoglobin levels provokes an enhancement of their productivity by 10–20% *(17–19).*

Regulation of Body Temperature

During iron deficiency and principally if it is associated with ferropenic anemia, a metabolic alteration takes place that reduces the ability to maintain the body temperature in a cold environment. Several studies performed in animal models and human beings demonstrated a metabolic alteration related to the secretion and utilization of thyroid hormones during iron deficiency. These hormones regulate the processes of thermogenesis of mammals, maintaining and controlling their body temperature; therefore, any alteration of the regulatory phases of the metabolism of these hormones may produce an alteration of the capability of the organism to regulate its body temperature *(20–22).*

Psychomotor Development

There is growing scientific evidence demonstrating the influence of anemia as a result of iron deficiency on the mental and the motor faculty of children. It is important to take into account that the increased prevalence of anemia takes place from 6 to 24 mo of age, which is coincident with cerebral growth and the acquisition of the cognitive and motor skills of the child. This agrees also with the fact that the greatest incorporation of iron into the brain takes place during the period of the highest growth rate of the nervous system. If this iron incorporation does not take place in this early stage of development, it seems difficult to restore the normal iron concentration in the brain during adulthood *(23).*

The neurophysiological and biochemical functions carried out by iron in the nervous system are based on its intervention in important processes, such as the production and maintenance of myelin, the regulation of the dopamine, serotonin, and GABA metabolisms, as well as the fact that iron integrates several enzymes related to the biosynthesis of neurotransmitters *(24).*

Several experimental studies, carried out in animal models and human beings, demonstrated that the anemia resulting from iron deficiency produces conduct and psychomotor changes. The work of Andraca et al. *(23)* and Lozoff *(25)* showed a decrease of mental development and motor faculty of "feeding milk" children with anemia as a result of iron deficiency; in the population with iron deficiency but with no anemia, these symptoms were not observed. On the other hand, even though there have been suggestions that the changes induced by anemia as a result of iron deficiency are irreversible, this has still not been clearly demonstrated and it is possible that this depends on the severity of the anemia, the degree of its chronic character, and the moment at which it appears *(23).*

Resistance to Infections

Several research groups studied the relationship between iron deficiency and the resistance to infections, obtaining different results, some of them contradictory *(26).* Even though some studies suggest that a slight iron deficiency might inhibit the development of pathogenic microorganisms, other studies suggest a lower resistance to infections in iron deficiency *(26).* In the case of human beings, Scrimshaw and San Giovanni *(27),* observed an alteration of the cellular and humoral immune system function during iron deficiency. However, even though there are different works suggesting a decrease of the incidence of infections during iron deficiency, there are no conclusive results on this point. Therefore, it can be assumed that the information concerning this subject is not complete at this moment and that further research on this matter is required *(28).*

Absorption of Toxic Metals

It has been found that iron deficiency, as well as the deficiency of different essential metals, produces an increased absorption of other metals, some of which are extremely toxic *(29).*

Different studies demonstrate that during iron deficiency, an increase of lead intestinal absorption takes place, which may provoke an important increase of the incidence of saturnism, especially in small children *(30).* Adults with iron deficiency may also suffer from lead poisoning, because the intestinal absorption of this metal is also significantly increased *(31).*

The absorption of cadmium and complexes of this toxic metal is also increased during iron deficiency. This situation may provoke a significant alteration of zinc metabolism, because cadmium is bound to the binding sites of metallothionein. This interference may cause significant changes in the metabolism and transport of zinc, which may produce significant alterations of children's growth *(29).*

During iron deficiency, an increased absorption of aluminum also takes place, which may interfere with calcium metabolism and cause consequent physiological alterations *(29).*

In this way, we may observe how the deficiency of some essential metals might cause toxic effects by increasing the absorption of certain toxic metals.

Pregnancy and Newborns

Iron deficiency affects most pregnant women. Those women beginning pregnancy with decreased iron stores and/or with an insufficient iron supply undergo a high risk of becoming iron deficient or getting anemia. The existing data suggest that iron deficiency during pregnancy affects both the health of the mother and that of the newborn *(32).*

In the mothers, anemia is associated with an increase in their death rate. Studies like those performed in England show that even moderate anemia is associated with an increase of the death rate; if the anemia is more serious, it causes one of every five maternal deaths. Even though the mechanisms of these effects have not been well established, a correlation between anemia and an increase of the incidence of heart insufficiency during labor, a smaller tolerance to blood loss during childbirth, a decreased resistance to infections, and a longer time for wound cicatrization was found *(19,32,33).*

Even though there is not much information about maternal morbidity associated with anemia caused by iron deficiency, two studies, one carried out in India and the other in the United States, demonstrated that pregnant women had low lymph cell stimulation indexes and a higher predisposition to infectious diseases; supplementation with iron improved the lymph cell stimulation significantly, which can be associated with an increase of the immune response and a better resistance to infections during childbirth *(32,34–36).*

Concerning the newborn's health, it has been demonstrated in a well-protocolized study that if the mother has anemia, the risk of premature childbirth increases 2.7 times; in the same way, newborns from anemic mothers weigh less than normal 3.1 times more frequently than from normal mothers. It has also be shown that serious anemia is responsible of the death of approx 30% of the hospitalized anemic children with no immediate blood transfusion; if the transfusion is carried out, they suffer other risks. On the other hand, another study performed in India demonstrated that those children born from mothers having anemia during their pregnancy showed a significantly decreased immune response, because they exhibited a lower blastogenic response to phytohemagglutinin (PHA), indicating a depression of the T-suppressor cell function *(19,35–37).*

Some studies confirm the hypothesis that the newborn's iron levels are related to the iron status of the mother and that the iron status of the mother–fetus unity is dependent on the ingested iron, which is necessary to prevent iron deficiency of the mother and the newborn *(38).* In this sense, the early studies performed by Strauss in 1933 showed that the red blood cell counts of newborns were not correlated to the mother's anemia at the moment of childbirth but at 1 yr of age; children born from anemic mothers showed half the hemoglobin concentration of those children born from nonanemic mothers *(32).*

Preziosi et al. *(39)* demonstrated that if mothers were supplemented with iron during their pregnancy, they did not suffer anemia, but those of the placebo group (with no iron supplementation) showed high anemia incidence. Newborns from anemic or nonanemic mothers did not show significant differences of the hematological values obtained from the umbilical cord blood; however, at 3 mo of age, the levels of serum ferritin were significantly higher in children born from nonanemic mothers. On the other hand, it could be shown that the anthropometrical parameters of children born from nonanemic mothers were significantly higher than those corresponding to children born from anemic mothers *(39).*

Moreover, Millman et al. found that children from mothers, who received iron supplementation and therefore were not anemic, showed significantly higher serum ferritin levels than those born from mothers who did not receive any iron supplements and, therefore, showed high anemia indexes *(40).*

These results showed a strong dependence of the iron status during pregnancy on the mother and the newborn health, as well as the consequent potential deleterious effects on the health of both if iron deficiency takes place during pregnancy.

Magnitude of the Problem

Even though it is difficult to evaluate the monetary cost representing the personal and social tragedy of the human losses caused by iron deficiency, the World Bank was able to estimate the losses caused by micronutrient malnutrition, among which iron deficiency has the highest prevalence. The cost of the resulting incapacities and deaths represent 5% of the Gross National Product (GNP) in those countries significantly affected by this deficiency *(19).*

STRATEGIES TO OVERCOME IRON DEFICIENCY

Even though the losses associated with micronutrient deficiency, especially that of iron, cause losses up to 5% of the GNP, considering incapacities and deaths, the solution of this problem has an economic cost of less than 0.3% of the GNP, representing a cost–benefit ratio of nearly 20 *(19,41).*

The solution and/or prevention of this problem, which has the best benefit–cost ratio, has been food fortification or pharmacological supplementation with one or more of the deficient micronutrients. Either procedure has advantages and disadvantages, which fundamentally depend on the physicochemical and biological properties of the micronutrient to be used, as well as the characteristics and habits of the population to which the procedure is to be applied *(19,41–43).*

Food fortification has been demonstrated to be an effective strategy. It consists in the addition of the deficient micronutrient to a food used as carrier, which has to be carefully selected, taking into account the eating habits of the population as well as the sector of the population considered as the risk group. This procedure has the fundamental advantage that the population, affected by a deficiency of a given micronutrient, will incorporate an additional quantity of it by means of the ordinarily consumed diet, with no change of the eating habits. However, the utilization of food fortification as a procedure should be considered as a prophylactic or preventive method to overcome the deficiency of a given micronutrient, particularly in the case of iron, because the fortification doses are generally a fraction of the daily requirements contained in the food portion. Therefore, this procedure should be considered as an intermediate or long-term strategy *(44–47).*

Another strategy is pharmacological supplementation, which is carried out by administering supplements, as, for example, iron, generally by oral pill intake. This therapy has to be applied particularly to those people who evidence iron deficiency or ferropenic anemia. In developed countries, this procedure is usually applied after an evaluation of the iron status by the determination of the corresponding biochemical parameters. However, in developing and in poorly industrialized countries, biochemical studies are not possible because of their high cost; they may be even more costly than the treatment itself. Therefore, in the developing regions in which high iron deficiency indexes exist, it is preferable to apply the treatment in a massive way to the population sector considered as the risk group without determining the biochemical parameters individually *(19,48,49).*

Currently, there exists a new concept called preventive supplementation, in which iron supplements are orally administered to those people who, even if they are not anemic, have a higher probability of getting it; this is the case of women of reproductive age who, in most of the cases, may be anemic or not but whose iron stores generally are very low. Therefore, in the case of pregnancy, they will be unable to face an increase of iron requirements because they will deplete their iron stores during the period of gestation or at the moment of the childbirth and they, generally, will get ferropenic anemia. In these cases, the preventive supplementation with iron has been demonstrated to be effective *(1,50,51).*

Even though oral iron administration is highly effective therapeutically, in the particular case of the massive application of this procedure to those populations largely affected by anemia, this method has been shown to be only slightly effective as a consequence of the lack of compliance of the people who have to take iron pills, owing to gastrointestinal side effects, such as diarrhea, constipation, epigastria, nauseas, meteorism, and so forth that may take place. Therefore, the use of new iron compounds with less toxicity and equal or higher bioavailability than that of ferrous sulfate, the ordinarily used agent, would be a highly useful tool to be used in this pharmacological procedure *(52–54).*

Moreover, this procedure has other disadvantages, which render it poorly effective when used widely. The supplement's supply and distribution limitations, the deficient capability of the health workers, the lack of coordination, and the poor education of the consumers, in addition to the lack of motivation of the involved health personnel, are all factors appearing generally in poorly industrialized or developing countries, which are those with the highest ferropenic anemia indexes. For these reasons, the use of supplements has an effectiveness that cannot be ensured. However, iron supplements are necessary and adequate in those cases in which high quantities of the metal are required, as, for example, in the case of pregnancy, especially in those women facing this situation without an adequate quantity of iron in their iron stores *(1,19,51,55,56).*

Therefore, the solution for iron deficiency is not simple, especially in those countries with poor economic resources and with high iron deficiency indexes. It is possible that the best solution is the simultaneous application of three strategies, each of which will have a longer-term objective than the previous one. First, as a short-term procedure, iron supplements should be administered rapidly and locally to the most affected groups. At the same time and as an intermediate-term strategy, adequate food fortification plans should be used, and, finally, it is necessary to apply educational programs to the population in order to modify their eating habits, a task that can take decades to accomplish. A national board whose responsibility should be the control of micronutrient deficiencies, the establishment of information webs, and the training of the personnel intervening in the area should coordinate the implementation of these measures synchronically. All of these efforts require a strong political commitment together with the support of an adequate infrastructure *(19,56–59).*

PHARMACOLOGICAL TREATMENT

The pharmacological treatment of ferropenic anemia is based on the administration of iron, generally orally, even though in some particular cases parenteral administration is more effective *(60).*

For oral treatment, ferrous sulfate is one of the most utilized iron salts. There are also other iron salts such as ferrous fumarate and ferrous gluconate, all of them being soluble in slightly acid aqueous media; for this reason, they all have a similar bioavailability. These salts are used for the production of pills, which have to be rapidly dissolved in the stomach because iron is absorbed mainly by the first portion of the small intestine *(54,61,62)*.

In order to increase the absorption of orally administered iron, helper substances, such as carbohydrates, amino acids, and vitamins, have been utilized in the production of the pills. Among these, ascorbic acid or vitamin C has demonstrated an important effect for increasing iron absorption. Unfortunately, together with the iron absorption increase, the secondary effects are also more important. Therefore, the utilization of these stimulants of iron absorption has little advantage *(63)*.

The orally administered iron dose during the treatment of ferropenic anemic is a practical compromise between the desired therapeutic effect and the side effects. Usually, the daily dose is divided into three intakes. As an example, in the adult the usual dose is about 200 mg of iron per day, which is supplied in three doses of 65 mg each. However, if the circumstances do not require urgency, the dose may be of about 100 mg of iron per day during longer periods. In the case of children, with weights between 15 and 30 kg, 50% of the adult dose is commonly used, with the same therapeutic scheme. Because younger children and those still feeding on milk have a higher tolerance to secondary effects, it is possible to use doses up to 5 mg of iron per day, an equivalent dose relatively higher than that for adults. In the case of the prophylactic administration of iron supplements, the doses are significantly lower, about 15–30 mg of iron per day *(54,64)*.

Usually, iron pills are to be taken between meals and not with them, as this can provoke an absorption decrease of the metal between 30% and 50%, depending on the meal composition. On the other hand, it has been observed that pharmacological doses of this metal may interfere with the absorption of other essential metals such as zinc *(54,65,66)*.

The duration of the treatment depends on the rate of hemoglobin concentration recovery and on the necessity to create new iron stores. In general, the recovery of normal hemoglobin levels takes place after the first 2 mo of treatment, depending on the iron dose and initial degree of anemia. However, the formation of iron storages is a more complex and difficult task, as once the normal hemoglobin levels have been established, the iron intestinal absorption decreases significantly. Consequently, the stores of this metal can be increased at a rate no greater than 100 mg of iron per month *(54)*.

The adverse effects usually observed during oral pharmacological treatment depend on the total mass of soluble iron in the upper portion of the digestive system as well as on psychological factors associated with the medicine intake. For example, with a usual dose of 200 mg of iron per day, an incidence of 24% of secondary effects are observed, whereas in the case in which a placebo is used, this proportion only reaches 13%. However, the secondary effects are dose dependent, because with the duplication of the iron dose, the secondary effects increase to 40%. The effects observed more frequently are nauseas and pain in the upper portion of the abdomen, pyrosis, and constipation or diarrhea, possibly associated with intestinal flora modifications. With liquid formulas, a transitory dental pigmentation can be observed, which can be avoided by depositing the iron solution on the rear portion of the tongue with a dropper *(54,67).*

The effectiveness of the parenteral administration is equivalent to that of the oral iron intake because the hemoglobin recovery rate is the same in both cases. An advantage of the parenteral iron administration is the fact that the formation of iron stores is achieved faster than in the case of oral iron supply. Therefore, parenteral iron administration is indicated, for example, in parenteral nutrition or in those cases in which iron cannot be given orally, as in sprue, in which iron intestinal absorption is impaired *(54,68).*

Parenteral iron administration can be carried out intramuscularly or intravenously. The second alternative is generally preferred owing to the local reactions at the injection site, which generally persist for long periods. Skin pigmentation at the injection point is also observed, which is troublesome because of the possibility of local malignant changes. On the other hand, the secondary effects associated with intravenous iron administration include headache, general malaise, fever, arthralgia, urticaria, and so forth. However, the anaphylactic reaction is the most troublesome secondary effect and, even if it is not frequent, it can cause death; therefore, there should be specific indications for iron parenteral administration *(54,60).*

Food Fortification

This procedure can be applied to certain sectors of the population considered to be risk groups, as well as to the whole population, incorporating this nutrient to a food usually consumed by the population. Consequently, the utilization of this method has the advantage that the individual does not need to remember everyday the necessity of the iron intake, which is the case with the pharmacological supplementation and which is frequently the cause for the failure of this procedure *(2,3,19,52).*

Foods Used as Carriers

Foods used as carriers for this mineral should comply with some requisites, the principal of which is that they have to be consumed widely by the risk groups. The foods principally used for this purpose are cereals and dairy products and, to a smaller extent, salt, sugar, and condiments *(44,69–71).*

Cereals

Cereals, their flours, and derived food products are the most frequent vehicles used for the fortification with iron as well as with other nutrients, because they are widely consumed by most populations. The products refined from cereals may be enriched with iron in order to restore the unrefined iron concentration of the whole grain (44 mg iron/kg). If the aim is to fortify with iron, the amounts should be substantially higher, generally in the case of wheat and corn flours, between 55 and 65 mg iron/kg are added. However, in some cereals designed for children, the iron content is significantly higher, being greater than 150 mg iron/kg in many cases *(19,46,72–76).*

One of the principal disadvantages of the utilization of flours as an iron carrier is its high phytic acid content, which is 1% in the whole grain and about 100 mg/kg in the refined flours. Phytic acid has a high inhibitory effect on iron absorption and, consequently, decreases its bioavailability *(77–80).*

Another disadvantage is that the presence of iron in flours and cereals increases their susceptibility to become rancid, because iron mediates the catalytic oxidation of their fats. To avoid this process, inert iron compounds such as ferric pyrophosphate or a fine powder of elementary iron are usually added, which has the disadvantage of having very low iron bioavailability. Therefore, it is necessary to add significantly higher iron quantities, which, in some cases, are of the order of 200 and 500 mg/kg; a promoter of iron absorption, such as ascorbic acid, also has to be added, because, if this is not done, the effectiveness of the fortification has to be considered doubtful *(71,81–83).*

Dairy Products

These foods as well as cereals and their derivatives are also considered as one of the principal vehicles to be fortified with iron and other micronutrients *(71).*

Children, one of the principal risk groups, largely consume fluid cow's milk in many countries. Infantile formulas are basically modified cow's milk with the addition of different nutrients. Milk with chocolate is an attractive vehicle to be fortified because children and adolescents largely consume it. Many maternal–infant programs in some developing countries distribute powdered milk freely, a reason why this product should be fortified with iron. Yogurts and fermented products, especially those of dietetic character, are widely consumed by women of reproductive age. The iron fortification of these foods would be an essential tool to overcome the deficiency of this micronutrient *(45,55,84–89).*

However, the fortification of dairy products and their derivatives with an element such as iron imply certain difficulties, owing to the complex composition of these foods and to the reactivity of iron, which causes the catalytic oxidation of fats, vitamins, and amino acids, producing a consequent rancidness and a decrease of the biological value of the food *(90,91).*

On the other hand, different nutrients present in dairy products, such as calcium, casein, serum proteins, and cacao in the case of milk with chocolate, cause a significant decrease of the iron absorption and, consequently, of its bioavailability. The addition of ascorbic acid has been demonstrated to be effective as a partial solution of this inhibitory effect. However, vitamin C in liquid media, as fluid milk, is rapidly degraded to diketogluconic acid, which makes the food less palatable *(92–106).*

Also in many countries, milk is consumed together with infusions like tea, coffee, or maté, which, once they come into contact with the iron used to fortify the milk, change the color of the liquid to black-grayish, making the food unappetizing *(71).*

The foregoing analysis demonstrates the usefulness of fortifying this food with a nutrient like iron, but, on the other hand, it also shows the problem of this procedure because of the high reactivity of iron. Therefore, the selection of an adequate compound of this metal is a must for the fortification of this particular food, as well as for all fortified foods in general.

Sugar

Sugar is another alternative that may be considered as a vehicle to be fortified with iron as well as with other nutrients such as vitamin A and zinc *(57,71,107,108).*

This is a food widely consumed by all the population segments, principally in those developing countries of the Caribbean and Central America that produce sugar. However, in other developing countries not producing this food, refined sugar is only accessible to the most favored economic sectors *(44).*

Technologically, the fortification of refined sugar is feasible and has no major drawbacks, because the utilization of different iron compounds did not cause significant changes in its color or texture. However, when less refined sugar is fortified with this metal, significant color changes were observed *(109).*

On the other hand, when sugar fortified with iron is added to certain infusions such as tea, coffee, maté, or to chocolate, a change of the normal color to black-grayish is produced, which makes the product unpalatable *(71).*

In refined sugar, there are no compounds that inhibit iron absorption and, consequently, decrease its bioavailability if sugar is fortified with iron. Notwithstanding, if the product is added to tea, coffee, or chocolate, the tannins contained in them will cause a significant decrease of the iron absorption. However, if this fortified food is used for the preparation of beverages or juices, principally of citric fruits, generally the iron absorption will strongly depend on the compound used as the fortifying agent. Therefore, the fortification of refined sugar with adequate iron compounds is to be considered an appropriate complementary procedure to overcome iron deficiency, especially in sugar-producing countries *(110,111).*

Salt

The fortification of salt with iodine has been demonstrated worldwide to be an effective strategy to overcome iodine deficiency. Therefore, salt could be an appropriate vehicle to be fortified with other micronutrients such as iron. However, it should be taken into account that in many developed and developing countries, salt consumption decreases steadily owing to health reasons; therefore, the choice of salt as a vehicle to be fortified with micronutrients raises questions of adequacy, at least in some sectors of populations.

Technologically, the fortification of salt with iron is faced with problems related to color changes. This effect is principally observed with poorly refined and highly humid salt, which is produced and consumed in developing countries *(19,112,113).*

To solve this problem, iron salts with low solubility such as ferric pyrophosphate have been used, but its bioavailability is very low; thus, monosodium sulfate has been added as an absorption promoter, which increases iron absorption by 80% *(112).*

Salt and ferric pyrophosphate have different grain sizes and densities. Therefore, the latter tends to deposit at the bottom of the flask, which causes an irregular iron intake. It has also been observed that when iron-fortified salt is used with some vegetable foods, color changes appear, making them less palatable *(71).*

Despite these problems, different studies performed principally in India showed that salt fortified principally with ferric pyrophosphate is an efficient fortification vehicle *(114–116).*

Condiments and Spices

Condiments and spices are an attractive vehicle to be used for iron fortification, especially in those countries in which they are usually consumed in large amounts. An example is India, a country with a high prevalence of anemia as a result of iron deficiency, which has a mean daily intake of 9.54 g of spices per capita *(19,117).* On the other hand, if the iron is supplied together with these species, its absorption is enhanced as a consequence of the stimulation of the gastric hydrochloric secretion provoked by these condiments *(118).*

Other condiments like curry, fish, or soy sauces and sodium glutamate are widely consumed in Asian countries. Their fortification with different iron compounds has been shown to be effective in decreasing the anemia indexes in the region *(71,117,119).*

Therefore, the utilization of condiments as vehicles for iron fortification is an effective alternative to overcome its nutritional deficiency in those countries in which they are consumed massively.

IRON COMPOUNDS USED AS FORTIFYING AGENTS

The choice of the compound to be used for fortification is based on its bioavailability, which depends, in part, on its solubility in the gastric juice. The changes of the physical characteristics of the food that may be produced as a consequence of the fortification have to be taken into account, also as well as the cost of the product used for this procedure *(4,120,121).*

Iron compounds may be classified from the practical viewpoint according to their solubility in aqueous media *(71,121,122):*

- Iron compounds very soluble in water:
  - Ferrous sulfate
  - Ferrous gluconate
  - Ferrous lactate
  - Ferric ammonium citrate
- Iron compounds slightly soluble in water but very soluble in diluted acid solutions such as gastric juice:
  - Ferrous fumarate
  - Ferrous succinate
  - Ferrous saccharate
- Iron compounds insoluble in water and poorly soluble in diluted acid solutions:
  - Ferric orthophosphate
  - Ferric ammonium orthophosphate
  - Ferric pyrophosphate
  - Elemental iron powder
    - Electrolytic
    - Carbonilic
    - Reduced iron
- Protected iron compounds:
  - Hemoglobin
  - EDTA–Fe(III)
  - Chelates of amino acids
  - Microencapsulated ferrous sulfate
  - Stabilized iron gluconates

Iron Compounds Very Soluble in Water

These compounds supply a highly bioavailable iron and, consequently, these compounds would be the primary choice to be used for food fortification. However, these compounds are highly reactive, causing oxidation of fats, some amino acids, and vitamins of the fortified food. Consequently, disagreeable changes in the food are produced, in addition to a decrease of its nutritional value *(71,90,91,121).*

These compounds are widely used to fortify solid dehydrated foods, which are stored in hermetical packing that isolates the content from humidity, as is the case in infant formulas. They can also be used to fortify flours and breads, which are rapidly consumed. Generally, these compounds cannot be used in liquid foods *(71,121,123,124).*

Cereals and derivatives as well as fresh dairy products fortified with these types of compounds are affected by their fat oxidation, causing rancidness a few days after the fortification procedure *(71).*

It should be noted that if many fortified foods such as salt, sugar, dairy products, and so forth are mixed with other foods containing polyphenols, such as tea, coffee, maté, and cocoa, they change the color of the food to black-grayish or violet tones, making the food unacceptable for consumption *(71).*

Therefore, even though from the point of view of their bioavailability, these compounds would be the best option to be used as food-fortifying agents, their high reactivity with nutritional matrix significantly limits their use.

Iron Compounds Slightly Soluble in Water but Very Soluble in Diluted Acid Solutions such as Gastric Juice

These compounds are less reactive than those highly soluble in water, but because they are dissolved completely in the gastric juice, they, consequently, have a high bioavailability *(71,121).*

These compounds have been demonstrated to be effective to fortify cereals because no problems of rancidness have been detected with them. They have been used also to fortify some infant formulas, as well as powdered cocoa. However, if they are used for wheat flour fortification, rancidness has been detected after a long storage period, probably due to humidity *(86,123,124).*

On the other hand, these compounds cannot be used in neutral liquid media because they will precipitate due to their poor solubility. Neither can they be used to fortify fresh dairy products, because the high humidity and high fat content cause the free-iron fraction to make the food rancid.

Even though these compounds offer technological advantages with regard to those compounds highly soluble in water, it is evident that proper gastric hydrochloric acid secretion is a limiting factor for their dissolution and absorption. In developing and in poorly industrialized countries, besides the high prevalence of iron deficiency, there are also high indexes (between 60% and 90%) of infection by *Helicobacter pylori.* This bacterium, which colonizes the stomach, in addition to causing different gastric pathologies, produces 40–50% of the cases of scarce or nil gastric hydrochloric secretion. Thus, it is uncertain if these compounds may be really effectively if used in those regions in which high iron deficiency indexes are combined with high *H. pylori* contamination rates *(125–128).*

However, recently several studies demonstrated that vitamin A and, even more, the β-carotenes increase the solubility of these compounds significantly even at practically neutral or slightly acid pH values (pH 6). This procedure decreases the inhibitory effect caused by the phytates and polyphenols that are present in the diet. Even if the mechanism by which these compounds exert this effect is not completely understood, it may be supposed that it takes place by means of the formation of complexes that would maintain the iron in a soluble form, precluding in this way the inhibitory effects of tannins and polyphenols on iron absorption. Therefore, certain foods such as cereals and their derivatives may be fortified with these compounds, adding also vitamin A or even better β-carotenes; this could be a successful strategy to increase the iron bioavailability of these compounds *(129–132).*

Iron Compounds Insoluble in Water and Poorly Soluble in Diluted Acid Solutions

These iron compounds are the most frequently utilized for food fortification. Their principal advantage is that they do not change the physical characteristics of the food. However, their principal disadvantage is their very low solubility in the gastric juice and, consequently, very low bioavailability *(121,133–135).*

This strong dependence of the solubility of these compounds on the gastric hydrochloric secretion is an important factor to be taken into account in those developing and nonindustrialized regions in which high rates of anemia as a result of iron deficiency are combined with high indexes of infection by *H. pylori.* Under these conditions the absorption of these iron compounds might be insignificant and, consequently, the fortification would be useless from the nutritional point of view *(126–128).*

Because these compounds have a low reactivity with the nutritional matrix, they are used to fortify a large variety of foods, especially cereals and flours, which have to be stored for long periods. However, several experimental studies showed that the absorption of these compounds *per se* is variable, being generally low, of the order of 5–40% with regard to that of ferrous sulfate. This wide range of absorption is a consequence of the variability of both the individual gastric secretion and the particle sizes of the compound, because for a given mass of a certain compound, the smaller the particle sizes, the greater the surface brought into contact with the gastric hydrochloric acid; consequently, the dissolution and absorption of the iron contained in the compound will be increased. However, as the particle sizes decrease, the price of the compound is increased, as well as the reactivity of the iron with the food. For these reason, the food industry generally uses iron compounds of larger particle sizes *(81,86,114,124,136–142).*

As a consequence of its low bioavailability, when these compounds are used to fortify some infant cereals, the amount of added metal is of the order of 200–550 mg iron/kg, together with sufficient quantities of ascorbic acid in order to enhance iron absorption *(46,71).*

On the other hand, Dunkel et al. *(143)* recently evaluated the genetic toxicity of elementary iron used for food fortification. The studies, carried out using mouse lymphoma L5178Y cells, showed the induction of a mutagenic response in the case of carbonilic iron with small particle sizes (mean size = 3 μm), but there was no response in the case of electrolytic iron, having larger particle sizes (mean size = 16 μm). These results indicate the necessity of carrying out complementary studies in order to evaluate the safety of the different iron compounds used for food fortification as well as for dietary and/or pharmacological supplementation *(143).*

Protected Iron Compounds

These compounds appear as a consequence of the necessity of using substances that supply highly bioavailable iron, like that of the compounds highly soluble in water but with a low iron reactivity with the nutritional matrix. These compounds are technologically adequate to be utilized in industrial procedures for food fortification *(121).*

Hemoglobin

This is a naturally protected iron compound that is present in the blood of different mammals. The iron of hemoglobin is protected from the surrounding medium by a tetrapyrrolic structure, forming the heme group, which is associated with a protein; this whole structure is the hemoglobin molecule *(144).*

The principal advantages of this iron compound are its high bioavailability even in the presence of other nutrients that may be found in the food, which inhibit iron absorption and that it is an inert iron compound with regard to its interaction with the nutritional matrix, because it does not cause the oxidation of vitamins or amino acids of the food or rancidness as a result of the oxidation of its fats *(74).*

One of its most important disadvantages is its intense red-brownish color and a very low relative iron content of only 0.34%. Thus, in order to supply iron quantities equivalent to those utilized for food fortification, it is necessary to add a large amount of hemoglobin to the food, which generally produces its intense color change. Another disadvantage is the necessity to obtaining enough blood in adequate hygienic conditions to use for the processes of food fortification *(74).*

As a consequence of its intense color, hemoglobin has only been used to fortify cookies, which have to be colored and made tastier with additives similar to chocolate, in order to mask the changes produced by their fortification. In a similar way, some infant cereals could be fortified. In all of the cases, the principal advantage was the high bioavailability of iron in the diet, approx 14–20%, in addition to a higher biological value of the food as a consequence of the increase of a high biological quality protein fraction *(72,74,145,146)*.

EDTA–Fe(III)

This is a chelate formed by ethylenediamine tetraacetic acid (EDTA) and iron in its ferric form. EDTA has the capacity to bind iron and many other cations by six unions, four with the carboxylic groups and the remaining two by means of coordinated bonds with the amine groups. EDTA–Fe(III) supplies nonhemic iron. During the digestive process in the stomach, iron remains strongly bound to EDTA, because its affinity constant is maximal at pH = 1; afterward, it is liberated in the intestinal lumen from which it is absorbed *(71,121,147)*.

The principal advantages of EDTA–Fe(III) when it is used for food fortification are, first, that the iron of this compound is protected from being bound to some inhibitors of nonhemic iron absorption such phytic acid, which is present in many cereals and legumes. In this way, the bioavailability of the supplied iron can be twice or nearly three times that of ferrous sulfate. However, in foods not containing absorption inhibitors, its bioavailability reaches only 30% of that of ferrous sulfate. EDTA–Fe(III) has been evaluated in different studies in which it was used to fortify sugar, curry, and fish sauce. All of the studies showed a positive effect on the nutritional iron status. Another advantage is its low interaction with the nutritional matrix, because it decreases almost totally the fat rancidness in cereals, a situation that is highly advantageous from the technological point of view *(108,117,147–152)*.

However, the principal disadvantage is its interaction with some components that are present in different foods, causing unacceptable palatability alterations. An example of this is the case of sugar fortifying, which, when it is added to tea, this infusion becomes black as a consequence of the polyphenols contained in it. Another case has been observed in the fortification of certain infant cereals, principally those containing banana extract, which changes to a violet color. In other foods containing starches, color changes as well as in some preparations containing cacao, which turn violet, have also been observed *(71)*.

Different speculations have been made concerning the interaction that EDTA–Fe(III) might exert on the absorption of other essential minerals, like Ca, Mg, Zn, and Cu. However, the quantities of EDTA–Fe(III) utilized for food fortification are some 50 and 80 times less than the nutritionally equivalent amounts of Mg and Ca, respectively. Thus, the influence of EDTA–Fe(III) on the metabolism of these cations is negligible. In the case of Cu and Zn, the situation is different because the ratio with Zn is equimolar, and in the case of Cu, EDTA–Fe(III) is equivalent to eight times the amount of Cu. However, it has been shown, experimentally but for unknown reasons, that EDTA–Fe(III) does not cause a negative effect on the metabolism of Cu and Zn, but to the contrary, it increases their absorption if they are present in the diet *(71,121,153).*

EDTA–Fe(III) has been demonstrated to be toxicologically safe. However, the capacity of this compound to increase the absorption of other metals present in the diet may be extended to toxic metals such as Hg, Pb, and Cd. The possible effect on the absorption of toxic metals is a factor that should be evaluated seriously before EDTA–Fe(III) is widely utilized for food fortification *(71,121,154,155).*

Amino Acid Chelates of Iron

In these iron compounds, the metal is protected from the external medium by means of its binding to two or three amino acid molecules, which is established with the carboxylic group by an ionic bond and with the amine group by a dative coordinated bond; in this way, a double heterocyclic ring is formed between the iron atom and the two amino acid molecules.

In the particular case of iron *bis*-glycine chelate, there are two glycine molecules participating in it, forming the previously mentioned ring. Different studies have shown that this particular compound exhibits contradictory results of its absorption mechanism, bioavailability, and interaction with other nutrients. For example, some authors postulate that this compound is not dissociated in the stomach as a consequence of the digestive processes but that it is absorbed by the dipeptide transport mechanism. On the contrary, Fox et al. *(156)* suggest that this compound is at least partially dissociated in the intestinal lumen and that it is absorbed in the same way as nonhemic iron. In the same manner, Pizarro et al. *(158)* demonstrated that the iron from this amino acid chelated compound is absorbed according to the nonheme iron pathway *(156–158).*

There are also large discrepancies with regard to the interaction that produces different enhancers and inhibitors on the iron absorption from this compound. As an example, it has been suggested that the compounds that usually inhibit nonheme iron absorption do not affect iron absorption from this chelate. However, Olivares et al. *(159)* demonstrated that fluid cow's milk produces a significant inhibition of the iron absorption from this compound and that ascorbic acid enhances it. In the same way, Fox et al. *(156)* demonstrated that the iron absorption from this chelate decreases as much as that of ferrous sulfate when it was supplied to children together with vegetable and cereal foods; these authors postulate that absorption inhibitors affect the iron of this compound in the same way as the nonheme iron of ferrous sulfate. However, Layrisse et al. *(160)* found that the use of this iron amino chelate would preclude, at least partially, the inhibitory effect of phytates *(135,157,161).*

It is still not clearly established whether this compound may produce palatability changes of the fortified foods or if it is stable when the foods fortified with it are submitted to different technological processes, which has to be known if this compound is to be used for large-scale food fortification. However, one of the principal advantages of this type of compound is that, unlike EDTA–Fe, it is composed totally by natural compounds that are usually present in foods and not by synthetic molecules.

Recently a new amino-chelated iron has begun to be studied. In this compound, the chelating agent is the amino acid glutamic acid that chelates the iron. However, this compound is still being studied in experimental animals. Future studies are awaited to understand the properties of this new chelate in order to be potentially used for food fortification *(162,163).*

The described situation demonstrates, therefore, the necessity of performing systematized and well-protocolized studies in order to establish clearly the biological behavior, as well as the nutritional characteristics and technological properties of this type of compounds before they are used for massive food fortification.

Microencapsulated Ferrous Sulfate

In this compound, the ferrous sulfate is protected from its environment by a membrane of phospholipids, precluding in this way its interaction with the food *(164–166).* This protected compound has been successfully utilized for several years to fortify fluid milk and dairy products by the food industry of Argentina, Australia, and Israel because, unlike the other iron compounds, it was conceived from the very beginning to be utilized for the fortification of this type of food.

The stabilized ferrous sulfate has been intensely evaluated with regard to its nutritional properties and its stability to industrial processes, showing a high bioavailability, low toxicity, and the same metabolic behavior as the iron from ferrous sulfate, as well as a good stability to the technological processes carried out for the industrial production of this type of food. However, this compound has the inconvenience of being much more expensive than nonencapsulated ferrous sulfate, which, in many cases, might be a limiting factor to its massive use as a food-fortifying agent *(105,121,167–177).*

Stabilized Iron Gluconates

There are two different types of stabilized iron gluconate; they are stabilized ferrous gluconate and stabilized ferric gluconate. In both cases, the iron is stabilized by means of a dative coordinated bound of the amine group of two or three molecules of glycine, respectively, and an ionic bound with the carboxylic group of two or three molecules of gluconate, respectively. That is why they cannot be considered as iron amino acid-chelated compounds. They were recently evaluated in experimental animal models, demonstrating that they have high iron bioavailability and low toxicity. From a technological point of view, they were experimentally used to fortify bread, cookies, powder milk, and different kinds of fruit juice without altering their physical characteristics. They are more expensive than nonstabilized ferrous and ferric gluconate but less expensive than other protected iron compounds. Nevertheless, much more research is needed before considering these iron compounds for massive use in food fortification *(178,179).*

MEASURING IRON ABSORPTION

The conventional chemical balance techniques measure the difference between the amount of mineral ingested and the amount in the feces. These methods have limited accuracy and validity besides being labor-intensive. By contrast isotope techniques directly and accurately measure iron and other mineral bioavailability from single foods and total diets, facilitate reliable evaluations of the numerous factors that influence mineral absorption, and help to identify those foods or fortificant-based interventions most likely to succeed in target populations. Stable isotopes are safe for use in children and pregnant women and feasible for field application. In the regions where food fortification is applied, the use of isotopic techniques is now well established for enhancing sensitivity of nutrition intervention trials.

Using the isotopic approach (in vivo and in vitro), determinations of bioavailability can be carried out. Laboratory assessment of iron availability (in vitro) by simulating human stomach measures percentage of iron that is potentially available and is the only rapid tool using radioactive isotopes to compare bioavailability from different foods and diets. It can also be used to investigate different promoters and inhibitors and the effect of food processing methods on iron bioavailability. The most common method (in vivo) is based on incorporation of radioactive (^{55}Fe and ^{59}Fe) and stable iron isotopes (^{54}Fe, ^{57}Fe, and ^{58}Fe) into red blood cells by means of the isotope food labeling and feeding to test subjects. Since newly absorbed iron is primarily used for hemoglobin synthesis, iron bioavailability from a specific diet can be determined simply by measuring the incorporation of an iron isotope into the red blood cell hemoglobin 14 d after the ingestion of the test meal *(180)*.

CONCLUSIONS

We may, therefore, conclude that nutritional iron deficiency is a worldwide problem impairing the health of the population as well as the economic progress of the regions significantly affected. Fortunately, the measures to solve this problem show a favorable effectiveness–cost ratio.

However, the application of these measures requires a concrete political decision and adequately coordinated flow of resources in order to achieve this objective.

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