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Fortification Strategies to Combat Zinc and Iron Deficiency

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Food fortification is an important strategy to combat iron and zinc deficiency. This review covers the basic concepts of food fortification, as well as its advantages and disadvantages. The main characteristics of the most common zinc and iron compounds used in this procedure are also analyzed.

Key Words: fortification, zinc, iron, micronutrient deficiency

Introduction

Deficiencies of vitamins and minerals can cause learning disabilities, mental retardation, poor health, low work capacity, blindness, and premature death. The result is a devastating public health problem, especially in developing countries. Deficiencies of vitamin A, iodine, and iron represent a loss in productivity of as much as 5% of the gross domestic product. Combating these deficiencies in a comprehensive and sustainable manner, however, would cost less than 0.3% of the gross domestic product.[1,2] The World Bank "World Development Report 1993" found micronutrient programs to be among the most cost-effective of all health interventions.[1] There are three types of approaches that can be used to improve micronutrient malnutrition management:

- Supplementation with pharmaceuticals dispensed in adequate forms.
- Fortification of food or water with nutrients.
- Consumer education and dietary change through the expansion of the demand for, and supply of, nutrient-rich food.

Although these options are all cost effective, developing countries have finite resources and must choose between the following options:[1]

- To aim their programs at specific subsets of the population (the poorest, pregnant women, newborns, preschool children, and/or the already ill) or at the whole population.
- To develop nutritional self-sufficiency through dietary change or to focus on the rapid supply of nutrients through fortification or supplementation.

Pharmaceutical supplementation involves the administration of supplements to individuals diagnosed with a certain micronutrient deficiency after a clinical and laboratory evaluation. In developing countries, these tests may be more expensive than treatment of the micronutrient deficiency itself. Pharmaceutical supplementation may therefore be applied to the whole population considered at risk of these deficiencies.[1,3,4] On the other hand, pharmaceutical supplementation programs have often failed owing to poor compliance, poor coverage, absence of commitment at the national and community levels, and poorly designed communications.[5]

Another option, food fortification the addition of specific nutrients to food or water, has been shown to be an effective strategy.[6–9] The success of fortification depends on the development of a product acceptable to the consumer and the government's ability to enforce adequate fortification policies. The scale of a fortification program is determined by the foods to be fortified and the proportion of the total food supply that are actually fortified.[1] The food vehicle should be carefully selected, taking into account food habits of the population as well as specific at-risk subsets of the population.[6–9] If a large proportion of the population is not at risk for a particular nutrient deficiency, therefore, one might want to select a food consumed by the needy and only by them. If the cost of fortification is low (and in most cases it is), however, extension of the fortification program to the entire population may be administratively more practical and still economically feasible.[1] Factors to be considered when a food product is fortified with a trace element include safety for the general population or specific subpopulations, beneficial effects of the fortification program, influence of the trace element on the organoleptic properties of the food, and cost of the fortification.[10]

The main advantage of fortification programs is that at-risk individuals consume additional quantities of the target nutrient by consuming their regular diet.[6–9] Forti-

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fication therefore does not require any changes in preexisting food beliefs and practices for the consumer and, unlike supplementation, fortification does not impose a burden on the health budget.[5] Successful fortification of a staple food may be one of the most equitable health interventions available, especially if the slight cost of the additional nutrients is absorbed by the state, because it reaches everyone including the poor, pregnant women, and young children—population subsets that social service can never cover completely.[1]

A quality assurance program is required to ensure the quality of the fortified food from production to consumption.[5] Both internal monitoring within the production plant and external monitoring by independent agencies are required; details of these strategies were summarized by Lofti et al.[11] Food fortification must be considered an interim strategy; it is a preventive method to combat micronutrient deficiencies.[6–9] Private sector involvement in fortification activities in many Latin American countries during the last few years suggests that it is time for a considerable expansion of fortification as a first approach to avoid micronutrient malnutrition. Fortification is only one aspect of a strategy, but by becoming commercially viable and sustainable, it can reduce the size of the at-risk population and the need for other measures such as pharmaceutical supplementation.[2]

Fortification Strategies to Combat Iron and Zinc Deficiencies

Fortification has the appeal of a panacea if the right food is selected; this allows high coverage of the population. Indeed, fortification has eradicated most vitamin and mineral deficiencies in industrialized countries. Unfortunately, an ideal food vehicle for fortification is not available in every situation. Nonetheless, many foods have successfully been fortified in a number of countries and, with dietary habits changing rapidly and food industries becoming more sophisticated, fortification is likely to be feasible in the near future in most countries. Fortified foods must be extensively tested in the developing phase to ensure manufacturing feasibility and consumer acceptance. Such testing, which includes availability, price, taste, appearance, and similarity to the unfortified product, is critical to ensure that the fortified food will not meet significant consumer resistance; if fortified products are even slightly off color, for example, they may be unacceptable to the consumer.[1]

Iron Fortification

The natural way to prevent iron deficiency would be to consume iron-rich foods, but when this is not possible food fortification can be an effective option. This strategy may be applied to at-risk groups or to the whole population through the addition of the nutrient to a food vehicle typically consumed by these individuals. Accordingly, this strategy has the advantage of not introducing a new daily behavior to the individual as in pharmacologic supplementation.[1,12–14] Iron compounds typically used for food fortification are inorganic iron compounds. The food vehicle must be carefully selected because its components may interfere with iron absorption and iron bioavailability.[15] On the other hand, at-risk groups must habitually consume the selected food vehicle. In this way, cereals, dairy products, and to a lesser extent sugar, salt, and condiments are the most commonly used products.[6,16,17] The selection of an iron compound to be used in food fortification is based on its bioavailability, which depends on its solubility in gastric juice, the presence of activators or inhibitors of iron absorption in the food vehicle, and the nutritional status of the individual. Possible changes in the food sensorial properties produced by the addition of iron, as well as the cost of the procedure, must be evaluated.[15,18] Fortification has been identified as one of the most cost-effective and sustainable approaches to controlling iron deficiency anemia.[2]

Iron Compounds

Iron compounds listed as generally recognized as safe (GRAS) by The U.S. Food and Drug Administration (FDA) include elemental iron, ferrous ascorbate, ferrous carbonate, ferrous citrate, ferrous fumarate, ferrous gluconate, ferrous lactate, ferrous sulfate, ferric ammonium citrate, ferric chloride, ferric citrate, ferric pyrophosphate, and ferric sulfate.[10]

Table 1 summarizes some iron compounds classified from a solubility point of view.[17] The iron in the first group of compounds, water-soluble compounds, are highly bioavailable, which makes them the first choice for food fortification. These compounds are highly reactive, however, catalyzing the oxidation of lipids, amino acids, and vitamins in the food vehicle, thereby modifying the sensorial characteristics of food and reducing its nutritional quality.[20–22] Such compounds are extensively used to fortify dehydrated solid foods including infant formulas. Occasionally they are used in liquid foods, but tend to cause an unacceptable metallic taste.[17,23,24] Cereals and milk products cannot be fortified with these salts because they provoke lipid oxidation.[17] Despite their high bioavailability, therefore, their reactivity involving the nutritional matrix significantly limits their uses.

The iron compounds in the second group are poorly soluble in water but soluble in a diluted acid solution. These compounds are less reactive than those already discussed and have high bioavailability because they are soluble in gastric juice.[17] Nevertheless, they cannot be used to fortify flours because they provoke rancidity after long periods of storage, most likely owing to their

Table 1. Iron Compounds Classified from the Practical Point of View of their Solubility

Group Characteristics	Examples
Iron compounds soluble in water	Ferrous sulfate
	Ferrous gluconate
	Ferrous lactate
	Ferrous amonic citrate
Iron compounds poorly soluble in water but soluble in diluted acid solutions	Ferrous fumarate
	Ferrous succinate
	Ferrous saccarate
Iron compounds insoluble in water and poorly soluble in diluted acid solutions	Ferric ortophosphate
	Ferric amonic ortophosphate
	Ferric pyrophosphate
	Elemental iron powder
	electrolytic
	carbonilic
	reduced
Iron-protected compounds	Hemoglobin
	EDTA-Fe (III)
	Amino acid chelates
	Stabilized ferrous sulfate

Source: adapted from reference 19.

humidity.[19,23] Additionally, they cannot be used to fortify liquid foods with $pH \cong 7$ because they precipitate.[19,23,24] Although these compounds have certain advantages compared with those in the first group, the normal secretion of hydrochloric acid by the stomach is a limiting factor for their solubility. When a fortification program is considered in developing countries, therefore, one must take into account the high incidence of *Helicobacter pylori* infection (60–90%), which provokes approximately 40% to 50% of achlorhydria.[25–27] In conclusion, although these compounds are less reactive, their solubility in the stomach strongly depends on the secretion of hydrochloric acid; they therefore may not be suitable for use in those regions where iron deficiency is combined with high rates of *Helicobacter pylori* infection.

The third group of iron compounds is more extensively used for food fortification because the compounds do not modify the sensorial characteristics of the food. These compounds are insoluble in water and poorly soluble in diluted acid solutions. The main disadvantage to these compounds is their poor solubility in gastric juice, which limits their bioavailability.[28–30] Normal secretion of gastric juice is also a limiting factor in the absorbability of these compounds; achlorhydria therefore interferes with the success of this fortification strategy.[25–27] Because of their low reactivity, these compounds are used to fortify cereals and flours. Numerous studies have shown inconsistencies in rates of absorption (5–40%) as compared with ferrous sulfate (a water-soluble compound). This may be explained by the variability of hydrochloric acid secretion in the stomach and by differences in the particle size of the compounds. When the particle size is smaller, the iron absorption is higher, but the product is also much more expensive.[17,19,24,31–37]

Whitaker reviewed the use of some iron compounds in food fortification.[10] He concluded that the use of elemental iron to fortify foods increased because it is inexpensive to produce and because organoleptic problems associated with it are minimal. The use of ferrous fumarate also increased because of its greater stability in foods compared with ferrous sulfate. Ferrous fumarate is relatively insoluble in aqueous solution but has a high bioavailability because it is soluble in acidic gastric juice. Even if there is a difference between the solubility of ferrous sulfate and ferrous fumarate in water, both compounds have similar bioavailabilities in normal human beings. Ferrous sulfate is more expensive than elemental iron and can catalyze the oxidation of fat-producing organoleptic problems in cereals during storage. Nevertheless, its use has also increased.[10]

Iron-protected compounds arose as a consequence of the need for high-bioavailability forms of iron with no reactivity with the nutritional matrix to be used in food fortification. Hemoglobin is the natural iron-protected compound; it has high iron bioavailability even in the presence of the food's inhibitory components, but it is intensely colored.[38–42] On the other hand, the hygienic conditions under which it is obtained can be a major problem to consider hemoglobin for use in food fortification.[41]

EDTA-Fe III also has high bioavailability even in the presence of inhibitors of iron absorption.[22,43–50] It has serious disadvantages such as the induction of color changes in some foods,[19] however, and raises the risk of absorbing toxic heavy metals such as cadmium, lead, and mercury.[17,51] Iron amino acid chelates have an advantage compared with EDTA-Fe (III): they are formed by natural compounds usually present in foods. However, there are no conclusive studies on the changes in bioavailability, sensorial food characteristics, or stability ascribable to different technologic procedures to which they are subjected during industrial food production procedures.

Stabilized ferrous sulfate is a ferrous sulfate stabilized by microencapsulation with phospholipids. The microencapsulation prevents iron from interacting with the nutritional matrix. This compound has been used successfully to fortify dairy products. This compound was intensively evaluated from technologic and nutritional standpoints; it is stable in industrial technologic processes and had high bioavailability, low toxicity, and the same metabolic behavior as iron from ferrous sulfate, but it is much more expensive than non-encapsulated ferrous sulfate.[52–58]

Zinc Fortification

Similar to food fortification in general, one of the critical factors for zinc fortification is selection of the food to be fortified. The ideal food vehicle is consumed throughout the year in quantities sufficient to provide adequate zinc to the population at greatest risk of zinc deficiency, but to place those who consume the food in larger quantities at no risk of toxicity. On the other hand, the selected food vehicle must be centrally processed, temperature stable, and technologically and economically fortifiable, and must not undergo changes in taste, texture, or appearance during storage. Successful fortification also depends on the availability of an appropriate fortifying agent; it must be readily absorbed and used, resistant to dietary inhibitors of zinc absorption, safe, stable, acceptable, and without effects on the organoleptic quality of the food vehicle.[5]

Until now, the major problem with zinc fortification was finding a suitable zinc compound.[59] Zinc sulfate and zinc oxide are the most commonly used zinc compounds for food fortification, but they have serious disadvantages. Zinc sulfate modifies food sensorial characteristics rendering food flavor unacceptable. Zinc oxide is insoluble and precipitates in liquid foods. In solid foods, granulometric and density differences between the particles of zinc oxide and solid food can cause zinc oxide to remain at the bottom of the package, not interacting with the nutritional matrix and not available for consumption.[59] For these reasons these compounds are used only in low quantities and in solid foods. In the case of zinc fortification, therefore, efforts should be made to develop protected fortifying agents, similar to those developed for iron.

Although micronutrient amounts added to cereals in most industrialized countries are generally based on restoration levels, zinc should be added at levels of true fortification because of the widespread nature of zinc deficiency throughout the world. Other factors to be taken into account when selecting the fortifying agent level are the consumption per capita of the food vehicle, the preparation and processing methods of the food vehicle, the dietary components that may modify (inhibit or enhance) the bioavailability of the fortifying agent, possible antagonistic interactions with other micronutrient-fortifying agents, prevalence of zinc deficiency within the target population, and estimated zinc requirement. At present, multiple micronutrient-fortifying agents that include zinc have been used in a limited number of food vehicles. Foods in the United States that are frequently enriched or fortified with zinc include flour, bakery products, breakfast cereals, cereals, macaroni, and infant formulas.[5]

Zinc Compounds

There is still much uncertainty regarding the best type of zinc compound to use as far as bioavailability, side effects, and technologic aptitudes.[5] There are five zinc compounds listed as GRAS by the FDA that may be used in fortifying foods: zinc sulfate, zinc chloride, zinc gluconate, zinc oxide, and zinc stearate.[10]

Both factors, zinc compound solubility-dissolution and intragastric pH, influence intestinal zinc absorption,[5] as do the side effects that zinc compounds provoke including unacceptable taste, nausea, dyspepsia, etc. Gastric pH is an important determinant of solubility: insoluble zinc compounds may be converted to zinc chloride in the gastric acid medium. Some investigators have therefore administered zinc supplements in orange juice or in a cola beverage to improve solubility of zinc. Poorer solubility with higher pH may be a considerable factor in populations in which gastric atrophy and achlorhydria are more prevalent owing to bacterial infections such as *Helicobacter pylori.*[25–27,60]

Zinc oxide is a commonly used source of supplementary zinc in diets of animals and humans.[2] In industrialized countries, zinc oxide is most frequently used for fortifying cereals. It is a cheap white powder that causes no organoleptic problems because it is added in very low quantities to solid foods only; it therefore does not interact with the nutritional matrix.[5,59] Zinc from zinc oxide has low bioavailability with regard to other dietary sources, however, and is prone to antagonistic reactions with other nutrients.[2] Zinc oxide has low to moderate bioavailability because it is insoluble in the basic pH of the small intestine, which prevents it from dissociating in the gastrointestinal tract.[5] This may also be the reason why fewer subjects reported undesirable side effects with zinc oxide than with other zinc compounds.[60] Nonethe-

Table 2. Zinc Compounds Used for Supplementation and Fortification

Zinc Oxide	Zinc Stearate
Zinc sulfate heptahydrate	Zinc ascorbate
Zinc chloride	Zinc picolinate
Zinc carbonate	Zinc aminoate
Zinc citrate	Zinc histidine
Zinc acetate	Zinc methionine
Zinc gluconate	Stabilized zinc gluconate

less, it is possible that zinc oxide's solubility could be improved with the addition of certain organic chelators such as cysteine.[5]

Zinc sulfate heptahydrate has also been used for fortifying blended foods. It is better absorbed than zinc oxide, but it is six times more expensive, it is not resistant to inhibitors, and it modifies the sensorial properties of the food vehicle giving foods an unacceptable taste.[5,53] Table 2 summarizes the most commonly used zinc compounds for supplementation or fortification.

Zinc acetate is recommended because it is well tolerated and readily absorbed, especially at low intragastric pH.[5] Zinc citrate was reported to have an unacceptable taste even when given in small amounts (3 mg zinc) in orange juice. Zinc methionine has a sulfurous taste in solution, which can be disguised by adding sugar, citric acid, and citrus flavor.[60] On the other hand, zinc methionine and zinc histidine were associated with increased urinary zinc excretion.[5]

A new zinc compound, a zinc gluconate stabilized with glycine, is now under study. It has the same bioavailability as zinc sulphate with the same metabolic behavior and similar toxicity values in rats. On the other hand, this compound has several important characteristics to be considered if used in food fortification: high solubility, soft taste, no modification of sensorial characteristics of food, and low cost.[59] Nevertheless, more research is necessary on the mechanisms underlying absorption and utilization of zinc to identify the most effective dietary zinc supplement.[5]

Iron-Zinc Interactions

Interactions between trace elements are primarily antagonistic. It is therefore expected that when two chemically similar ions are present in the intestinal lumen, the one having greater molar ratio will tend to exclude the other. In terms of dietary intake, recommendations for iron (10 mg) and zinc (15 mg) in adult males are on the same order of magnitude. However, nutrient supplements generally provide iron at much higher amounts than zinc. Issues of interference of iron on the absorption of zinc reflect the dominant reality.[61] Many studies have shown that high concentrations of iron could have a negative effect on zinc absorption in human adults when zinc and iron are given in a solution. When given in a meal, however, such an effect is not observed, possibly because zinc can be absorbed via an alternate pathway with the aid of ligands formed during digestion.[10] On the other hand, amounts of iron and zinc should be determined by finding the optimal ratio to avoid antagonistic interactions between them. In this sense, many investigators recommend the addition of iron and zinc in a 1 to 1 molar ratio. It has been found that 12 mg of each metal is considered the appropriate amount to obtain the best results.[62]

Conclusion

Food fortification is an efficient procedure in the prevention of iron and zinc deficiency. The use of some protected iron and zinc compounds allows us to fortify different foods without altering the sensorial properties of the fortified food. However, these protected iron and zinc compounds must be carefully selected according to the composition of the nutritional matrix as well as the technologic processes they have to use during production of the fortified food.

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