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Iron and zinc interactions in humans[1,2]

Paul Whittaker

ABSTRACT Iron deficiency is the most common nutritional deficiency in the world; zinc deficiency is associated with poor growth and development and impaired immune response. Several Third World countries are taking measures to increase the dietary intake of iron and zinc with fortification of foods or dietary supplements. Several studies showed that high iron concentrations can negatively affect zinc absorption in adults when these trace minerals are given in solution. However, when iron and zinc are given in a meal, this effect is not observed. Solomons (J Nutr 1986;116:927–35) postulated that the total amount of ionic species affects the absorption of zinc and that a total dose of >25 mg Fe may produce a measurable effect on zinc absorption. This could occur if iron supplements are taken with a meal, and iron experts recommend that iron supplements be taken between meals. Recent studies using stable isotopes showed that fortifying foods with iron at current fortification amounts has no adverse effect on zinc absorption. There are 5 zinc salts listed as generally recommended as safe (GRAS) by the US Food and Drug Administration for food fortification. From 1970 to 1987, the total amount of zinc salts used in food continually increased, with zinc oxide and zinc sulfate showing the largest increases. Twelve iron sources are listed as GRAS; elemental iron has become the source of choice because it is less expensive to produce and has fewer organoleptic problems. Use of ferrous fumarate is also increasing. *Am J Clin Nutr* 1998;68:442S–6S.

KEY WORDS Iron, zinc, interactions, absorption, fortification, human, supplements

INTRODUCTION

Deficiency of trace minerals in humans may be a result of inadequate intake of the mineral in the diet or decreased or impaired absorption in the presence of adequate dietary intakes. Factors that decrease or impair absorption include dietary constituents, such as phytate or fiber, drugs or other chemicals that may interact with the essential trace minerals; and interactions between essential nutrients. Chemically similar elements may share a pathway for absorption, thus resulting in competition for uptake into the mucosal cells (1, 2).

Iron deficiency, whether resulting from inadequate intake or decreased absorption, is the primary cause of nutritional anemia and the most common nutritional deficiency in the world. Reducing the high incidence of iron deficiency anemia is important because of the association, in the first few years of life, between learning capacity and cognitive performance and iron deficiency anemia. Iron absorption can be increased by increasing dietary factors that enhance iron absorption (ascorbic acid and meat), by decreasing factors that inhibit iron absorption (phytate and phenolic compounds), or by increasing the iron content of the diet by fortification or supplementation. If the prevalence of iron deficiency anemia is high in a population, specific subpopulations can be targeted for iron supplementation. For example, iron supplementation is commonly required during pregnancy because most women have limited iron stores to meet the high iron demands.

Because a sensitive indicator for determining zinc status has not been developed, the requirement and recommended dietary allowance has been established with uncertainties. Zinc deficiency is associated with poor growth, loss of appetite, skin lesions, impaired taste acuity, delayed wound healing, hypogonadism, delayed sexual maturation, and impaired immune response. Zinc status is regulated by strong homeostatic control of absorption and excretion (3). Zinc is more efficiently absorbed in small amounts than in large amounts, and individuals having a poor zinc status absorb zinc more efficiently than those with a good status (3). Zinc deficiency resulting from reduced zinc absorption has been observed in children in rural areas of Iran and Egypt because their diets, although containing acceptable amounts of zinc, had high amounts of inhibitors such as fiber and phytate (4). In cases such as these, the children responded to zinc supplementation with improved growth. Prasad (4) recommended that diets be improved with bioavailable forms of zinc or by fortification of a food with a zinc salt.

Several studies have described the effects of iron on zinc absorption. The results appear to be conflicting, and the negative effect of iron on zinc absorption reported in some of the studies raised concern about possible adverse effects of fortifying foods with iron, as well as the effect of taking iron supplements on zinc absorption. The lack of a suitable index or indexes for measuring body zinc concentrations is a troubling problem and is of concern to many investigators. It has been found in several studies (1, 5–7) that iron supplementation resulted in lower plasma zinc concentrations, but plasma zinc concentration is not considered

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[1] From the Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC.

[2] Address reprint requests to P Whittaker, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 200 C Street, SW Washington, DC 20204. E-mail: pvw@cfsan.fda.gov.

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to be a good index of body zinc. Any conclusions regarding the effect of iron supplements on zinc status are difficult to make with certainty because the results could reflect a redistribution of zinc within the body as a result of taking supplemental iron.

IRON AND ZINC STUDIES

In 1981 Solomons and Jacob (5) measured iron and zinc interaction in humans. Subjects ingested 25 mg Zn alone in a cola beverage or with 25, 50, or 75 mg Fe, and changes in plasma zinc concentrations were determined. As the ratio of dietary iron to zinc increased (0, 1:1, 2:1, and 3:1), plasma zinc concentration decreased. No effect on zinc absorption was observed with heme iron at a 3:1 iron to zinc ratio, and absorption of zinc from oysters (54 mg Zn) was not inhibited with 100 mg Fe.

Solomons et al (6) also measured iron and zinc interaction in humans after oral ingestion of 25 mg Zn alone or with 50 mg Fe^{2+} or Fe^{3+}. Fe^{3+} in a 2:1 iron to zinc ratio reduced the plasma uptake of zinc, but to a significantly lesser degree than did Fe^{2+}. Addition of 1 g ascorbic acid increased the inhibitory effect of Fe^{3+} to that of Fe^{2+}. Meadows et al (7) investigated the effect of a daily oral supplement of 100 mg Fe, 50 mg Zn, and 350 μg folic acid for 14 d in healthy nonpregnant adults and found a significant reduction in plasma zinc after the 14-d supplementation.

The effect of iron on zinc absorption has also been measured by radioisotopic labeling, followed by measurements of whole-body retention of ^{65}Zn ($ZnCl_2$). Valberg et al (8) measured retention after 7 d and found that zinc absorption was inhibited by inorganic and heme iron when the iron was given in water but not by iron incorporated into a turkey meal. In another study, Sandstrom et al (9) found that increasing the molar ratio of iron to zinc from 1:1 to 2.5:1 did not affect absorption of zinc from water. An iron to zinc ratio of 25:1 decreased zinc absorption, but addition of the zinc ligand histidine decreased the inhibitory effect of this dose of iron and zinc absorption increased from 34% to 47%. Sandstrom et al also observed no inhibitory effect on zinc absorption when iron and zinc were given with a meal of rice and meat sauce. In a recent study, the effect of iron fortification on the absorption of zinc was studied by using radioisotopic labeling of single meals, followed by measurements of whole-body retention of ^{65}Zn (10). No significant differences in zinc absorption were observed in adult males consuming iron-fortified weaning cereal, bread rolls, or infant formula when compared with those consuming the unfortified counterparts.

Metabolic balance studies have been performed with infants to determine whether iron fortification of infant formulas has an effect on zinc absorption (11). Two infant formulas of identical composition except for iron concentration (10.2 and 2.5 mg Fe/L) were used. The zinc concentration was 1.9 mg/L and the iron to zinc ratios were 5.4:1 and 1.3:1, respectively. No significant effect on zinc absorption was observed. With the formula containing 10.2 mg Fe/L, zinc absorption was 15.6%; with 2.5 mg Fe/L, absorption was 20.3%.

Studies were carried out to determine the effect of zinc on the absorption of iron. Crofton et al (12) used radiolabeled iron and unlabeled iron in a single oral dose to measure plasma iron concentrations in healthy male volunteers. In their first study, there was no effect of 344 μmol (22 mg) Zn on the absorption of 842 μmol (47 mg) Fe, using radiolabeled iron (^{59}Fe). In a subsequent study, a significant reduction of plasma iron was observed with iron to zinc ratios of 1:1 and 1:2.5. Another study by Rossander-Hultén et al (13), measured the effect of zinc on iron absorption in human subjects with use of a dual-radioisotope method (^{55}Fe and ^{59}Fe). When given in water, a 5-fold ratio of zinc to iron reduced iron absorption by 56%; however, fortification with zinc up to a ratio of 1:5 (iron to zinc) given in a hamburger meal did not interfere with iron absorption.

A summary of studies (2, 5–13) examining the effects of iron and zinc interaction in human subjects is presented in **Table 1**. Most infant formulas in the United States contain ≈5 mg Zn/L and ≈12 mg Fe/L (14). The phytate in soy formula reduces zinc bioavailability, and Lönnerdal (14) recommended that zinc be increased to 7 mg/L. Formulas should be supplemented with iron because of iron deficiency after 4 mo (14). Infants receiving a milk formula with 7 mg Fe/L have satisfactory hematologic indexes. Lönnerdal suggested that this amount of iron would give an iron to zinc ratio of ≈1:1, which may exclude the possibility of an interaction between iron and zinc (14).

ZINC AND IRON FORTIFICATION OF FOOD

Factors to consider when a food product is fortified with a trace element include safety for the general population or specific subpopulations, beneficial effects of the trace element fortification, influence of the trace element on the organoleptic properties of the food, and cost of the fortification. Addition of nutrients to specific foods has been effective, but public health authorities are concerned that random fortification of foods could produce nutrient imbalances or excesses. The US Food and Drug Administration (FDA) encourages the prudent use of nutrients as additives to foods and does not consider it appropriate to fortify meat, poultry, or fish products; sugars; or snack foods such as candies and carbonated beverages. Foods commonly fortified with metals in the United States include flour, bakery goods, rice, macaroni products, breakfast cereals, and infant formulas (15). The metals used for fortification of food are classified by the FDA as generally recognized as safe (GRAS). GRAS classification may be based only on the recommendations of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. These recommendations may be based on scientific procedures that use the same quantity and quality of evidence required to obtain approval for a food additive, or the substance's demonstrated safety through its use in food before January 1958 (15). An ingredient not in common use in food before January 1958 may achieve GRAS status only through scientific procedures (15).

There are currently 5 zinc salts listed as GRAS that may be used in fortifying foods. They are zinc sulfate, zinc chloride, zinc gluconate, zinc oxide, and zinc stearate (15). The amounts of zinc compounds used by food manufacturers in the United States were compiled by the National Academy of Sciences (16). Only 2 zinc compounds, zinc sulfate and zinc gluconate, have usage data from 1970 to 1987. During this period, the use of zinc sulfate increased 27-fold and that of zinc gluconate increased 3-fold. The first use of zinc oxide in food was noted in the 1975 survey and by 1987 its usage had increased ≈9-fold. From 1970 to 1987, the quantity of zinc salts used in food has continually increased. The total amount of zinc compounds in the US food supply in 1970 was 5830 kg; by 1987 it increased 32-fold to 187 149 kg. The most significant increase was in the use of zinc oxide, and then zinc sulfate (**Table 2**).

TABLE 1

Summary of studies examining the effects of iron and zinc interaction in human subjects[1]

Reference	Iron	Zinc	Fe:Zn	Carrier	Effect
	mg	*mg*			
Solomons and Jacob, 1981 (5)	25	25	1:1	Cola	D
Solomons and Jacob, 1981 (5)	50	25	2:1	Cola	D
Solomons and Jacob, 1981 (5)	75	25	3:1	Cola	D
Solomons and Jacob, 1981 (5)	100	54	1.9:1	Oysters	NE
Solomons et al, 1983 (6)	50	25	2:1	Cola	D
Aggett et al, 1983 (2)	47	22.5	2:1	Water	D
Meadows et al, 1983 (7)	100	50	2:1	Water	D
Valberg et al, 1984 (8)	51	6	10:1	Water	D
Valberg et al, 1984 (8)	26	6.2	5:1	Water, heme	D
Valberg et al, 1984 (8)	17	4	5:1	Turkey	NE
Valberg et al, 1984 (8)	34	4	10:1	Turkey	NE
Sandstrom et al, 1985 (9)	2.2	2.6	1:1	Water	NE
Sandstrom et al, 1985 (9)	5.6	2.6	2.5:1	Water	NE
Sandstrom et al, 1985 (9)	56	2.6	25:1	Water	D
Sandstrom et al, 1985 (9)	2.2	2.6	1:1	Rice and meat	NE
Sandstrom et al, 1985 (9)	5.6	2.6	2.5:1	Rice and meat	NE
Sandstrom et al, 1985 (9)	56	2.6	25:1	Rice and meat	D
Haschke et al, 1986 (11)	2.5[2]	1.87[2]	1.3:1	Infant formula	NE
Haschke et al, 1986 (11)	10.2[2]	1.88[2]	5.4:1	Infant formula	NE
Crofton et al, 1989 (12)	47	22	2.4:1	Water	NE
Crofton et al, 1989 (12)	24	27	1:1	Water	D
Crofton et al, 1989 (12)	24	68	1:2.5	Water	D
Rossander-Hultén et al, 1991 (13)	3	15	1:5	Water	D
Rossander-Hultén et al, 1991 (13)	3	45	1:15	Water	D
Rossander-Hultén et al, 1991 (13)	3	15	1:5	Hamburger	NE
Davidsson et al, 1995 (10)	10.3	0.44	23.3:1	Weaning cereal	NE
Davidsson et al, 1995 (10)	25.3	0.44	57.4:1	Weaning cereal	NE
Davidsson et al, 1995 (10)	4.5	0.51	8.8:1	Bread rolls	NE
Davidsson et al, 1995 (10)	5.5	0.54	10.2:1	Infant formula	NE

[1] D, decreased zinc absorption; NE, no effect on zinc absorption.
[2] Iron and zinc expressed as mg/L.

In the United States, 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 have been affirmed by the FDA as GRAS and can be used for food fortification (15). The amounts of iron and iron salts used by food manufacturers in the United States were also compiled in surveys by the National Academy of Sciences (16). Iron usage based on surveys conducted between 1970 and 1987 is listed in **Table 3**. During this time, the amount of elemental iron consisting of both reduced and electrolytic iron added to food increased 120-fold (from 84 262 to 10 147 218 kg) and ferrous fumarate increased ≈40-fold (from 1398 to 54 934 kg). In contrast, ferrous sulfate, ferric phosphate, and ferric pyrophosphate decreased by more than 30%, 40%, and 90%, respectively. The use of elemental iron in fortifying foods has increased because it is inexpensive to produce and because organoleptic problems associated with it are minimal. Ferrous fumarate use has increased because of its greater stability in foods compared with that of ferrous sulfate; ferrous fumarate is only slightly soluble in water compared with ferrous sulfate, which is highly water soluble. Even with this difference in aqueous solubility, the compounds have similar bioavailabilities. The total amount of iron compounds in the US food supply in 1970 was 543 768 kg; by 1987 it increased 19-fold to 10 367 953 kg.

TABLE 2

Amount of zinc compounds in the US food supply in the years surveyed by the National Academy of Sciences[1]

Zinc fortificant	Amount of zinc used				
	1970	1975	1976	1982	1987
			kg		
Zinc chloride	ND	ND	ND	10	10
Zinc gluconate	3024	ND	10578	2629	9171
Zinc oxide	ND	5448	42177	33551	102150
Zinc stearate	ND	ND	ND	218	ND
Zinc sulfate	2806	12485	2992	37183	5818

[1] Data from reference 16. ND, no data available.

DISCUSSION

Several publications have described the effects of iron on zinc absorption, and many of the results appear to be conflicting (Table 1). In the early studies (5–7), high supplemental doses of zinc were given and serum or plasma zinc concentrations were measured to determine the effect of iron on zinc absorption. It should be noted that there are limitations to these studies, because measurement of circulating concentrations did not necessarily indicate the net zinc uptake, and the dose of zinc administered was much higher than the amount in a normal meal. In

TABLE 3

Amount of iron compounds in the US food supply in the years surveyed by the National Academy of Sciences[1]

Iron fortificant	Amount of iron used				
	1970	1975	1976	1982	1987
			kg		
Reduced iron	72 186	303 726	142 102	171 612	10 124 200
Electrolytic iron	12 076	ND	46 762	81 266	23 018
Ferrous sulfate	267 406	163 894	212 018	328 696	83 082
Ferrous fumarate	1398	ND	5312	15 618	54 934
Ferrous gluconate	10 578	ND	6946	2760	9262
Ferric ammonium citrate	13 983	ND	2157	713	ND
Ferric phosphate	165 710	175 244	103 512	319 162	73094
Ferric pyrophosphate	431	15	10	681	363

[1] Data from reference 16. ND, no data available.

other studies the effect of iron on zinc absorption was determined when zinc was given with differing amounts of iron in single test meals or oral doses (8, 9). Because the body can regulate zinc excretion and absorption to maintain zinc homeostasis under various dietary conditions, adaptive mechanisms may compensate for adverse effects of iron and zinc absorption from single test meals (17). Studies showed that high concentrations of iron can have a negative effect on zinc absorption in human adults when the zinc and iron are given in solution (8, 9). However, when given in a meal, such an effect is not observed. It has been suggested that suppression of zinc absorption by iron occurs when given in an aqueous medium because of competition for a common nonspecific pathway. This may not occur when zinc can be absorbed via an alternate pathway with the aid of ligands formed during protein digestion (9).

Solomons (1) postulated that the total amount of ionic species determines the effect on absorption of zinc, and that a total dose of iron >25 mg may produce a measurable effect on zinc absorption. Because of this iron and zinc interrelation, there is concern about taking iron supplements with meals and significantly increasing iron concentrations. To avoid this problem and to keep iron below 25 mg, it is recommended that supplements be taken between meals. It appears, however, that fortifying foods with iron does not affect zinc absorption when lower fortification amounts of iron are used. In a recent study using radioisotope labeling, no adverse effect was observed on zinc absorption when iron was added to bread rolls, infant formula, and weaning foods at the current fortification amount (10).

Although 5 zinc salts are listed as GRAS for use in food fortification, no zinc compounds have been affirmed by the FDA as GRAS for direct addition to food. During the period from 1970 to 1987, there was a continual increase in the total amount of zinc salts used in food (Table 2). The total quantity of zinc salts used in 1970 was 5830 kg and it increased to 187 149 kg in 1987. The most significant increase was observed with zinc oxide and then zinc sulfate.

Elemental iron has become the iron source of choice for food fortification in the United States because it is less expensive to produce and has fewer organoleptic problems than ferrous sulfate. As shown in Table 3, there has been a steady increase in the quantity of elemental iron used in food. The amount used by food manufacturers in 1982 was 252 878 kg and by 1987 this had increased to 10 147 218 kg. During the same period, usage of ferrous sulfate and ferric phosphate each declined by ≈75%. Although ferrous sulfate has a higher bioavailability than elemental iron, it is more expensive and can catalyze the oxidation of fat and produce organoleptic problems in cereals during storage. Use of ferrous fumarate has also been increasing but at a much more moderate rate than use of elemental iron. This iron salt is relatively insoluble in aqueous media but has a high bioavailability because it is soluble in acidic gastric juice.

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