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Acute inhibition of iron bioavailability by zinc: studies in humans

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Abstract Iron (Fe) and zinc (Zn) deficiencies constitute two of the most important nutritional and public health problems affecting developing countries. Combined supplementation or fortification with Zn and Fe are strategies that can be used to improve the Zn and Fe status of a population. However, there is concern about potential negative interactions between these two micronutrients due to a competitive binding to DMT1 and Zip14 transporter. Studies performed in humans have shown an inhibitory effect of Zn on Fe absorption when both minerals are given together as a solution in fasting conditions. We found that at low doses of iron (0.5 mg) the threshold for the inhibition of iron bioavailability was at a Zn:Fe wt/wt ratio ≥5.9:1, whereas at higher doses of Fe (10 mg) this inhibition occurred at 1:1 Zn:Fe wt/wt ratio. This differential response could be explained by the variation in the abundance of both cations as they compete for a limited number of shared transporters at the enterocyte. Conflicting results have been obtained when this interaction was studied in different food matrices. A negative interaction was not observed when Fe and Zn were provided in a composite hamburger meal, premature formula, human milk, or cow milk. A decrease on Fe absorption was observed in only 1 of 3 studies when Fe and Zn were supplied in wheat flour. The possibility of a negative interaction should be considered for supplementation or fortification programs with both microminerals.

Keywords Iron absorption · Zinc · Iron · Interactions · DMT1 · Humans

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Introduction

Iron (Fe) and zinc (Zn) nutritional deficiencies constitute two of the most important nutritional and public health problems affecting developing countries (McLean et al. 2007 International Zinc Nutrition Consultative Group (IZiNCG) 2004). Combined supplementation or fortification with both microminerals are strategies used to combat these deficiencies. However, a potential problem with these interventions is a possible mutual negative interaction at the absorptive level between these minerals.

The effects of Fe on the absorption of Zn have been extensively studied (Whittaker 1998). These studies have shown that when both minerals are delivered in an aqueous solution or in simple food matrix Zn absorption is decreased in a dose dependent way when the Fe to Zn wt/wt ratio is >2:1. Conversely in complex food matrices this inhibitory effect is not seen except at >25:1 Fe:Zn wt/wt ratio.

Scarce studies have assessed whether simultaneous administration of Fe and Zn either as a supplement or as a fortified food affects Fe absorption. Studies in vitro have demonstrated an inhibitory effect of Zn on Fe uptake (Tallkvist et al. 2000; Wien et al. 1994; Arredondo et al. 2006; Abd Rashed 2011). We have shown that there is a decrease in the uptake of 5 μM of Fe in Caco-2 cells, a human epithelial intestinal cell line, when incubated with graded doses of Zn (2.5–1,000 μM), and that a 50% inhibition of Fe uptake is observed at a Zn:Fe molar ratio of 1.7:1 (Arredondo et al. 2006).

The aim of the current review was to summarize the published acute effects of Zn on Fe absorption in humans.

Effect of Zn given in saline or aqueous solutions or as a supplement on Fe absorption

Seven studies have addressed this issue (Table 1). All studies were performed with subjects in fasting condition.

The first study looking at the effect of Zn on Fe absorption was published by Crofton et al. (1989). The authors used the Fe post absorptive curve (AUC) as a surrogate of Fe absorption. Aqueous solutions (125 ml) were administered to subjects using a crossover design. In the first experiment, nine adult males, received solutions containing either 47 mg of Fe alone or the same amount of Fe plus 22.5 mg of Zn, and no statistically significant change was found in the AUC, 3 and 6 h post administration. In the second study, seven adults received solutions containing either 23.5 mg of Fe or the same amount of Fe plus either 27.5 mg or 68.5 mg of Zn. A 66 and 80% mean reduction in the AUC was found at a Zn:Fe wt/wt ratio of 1.2:1 at 3 and 6 h, respectively. The mean reduction for a Zn:Fe wt/wt ratio of 2.9:1 was 72 and 90%, respectively. All these changes were statistically significant.

A few years later the effect of Zn on Fe absorption was assessed by measuring Fe bioavailability on the basis of erythrocyte incorporation of either ^{55}Fe or ^{59}Fe (Rossander-Hulten et al. 1991). Female adult subjects ($n = 9$) received 10 ml of aqueous solution containing 3 mg of Fe or 3 mg of Fe plus 15 mg of Zn. Fe absorption without Zn was 22.9 ± 3.5% and with Zn was 12.5 ± 4.0% ($p < 0.001$). A second study was performed in three men and seven women, but Zn content of the solution was increased to 45 mg. Fe absorption was 11.1 ± 2.5% and 24.9 ± 4.1% with and without Zn, respectively ($p < 0.001$).

A significant reduction of Fe absorption was observed in five preterm infants aged ~1 month, when they received, between feeds, 1–2 ml of a saline solution containing 0.3 mg/kg of Fe and 1.2 mg/kg of Zn [3.6% (range ± 1 SD: 2.6–5.1)] compared to the absorption of the same solution containing 0.3 mg/kg of Fe and 0.3 mg/kg of Zn [7.5% (5.7–10)] (Friel et al. 1998).

Fe absorption did not differ between pregnant women ($n = 14$ subjects per group) receiving either a prenatal supplement containing 60 mg of Fe and 250 μg folate or the same supplement with 15 mg of Zn (O'Brien et al. 1999).

Studies from our group have shown that there is no significant effect of Zn on the absorption of 0.5 mg Fe when both minerals are provided in 50 ml of water at Zn:Fe wt/wt ratios up to 2.3:1, but a dose dependent inhibitory effect is found at wt/wt ratios ≥ 5.9:1. Fe absorption was decreased by 28, 30 and 40% at 5.9:1, 11.6:1 and 23.4:1 Zn:Fe wt/wt ratios, respectively (Olivares et al. 2007a). Furthermore, we have shown that the effect not only depends on the Zn:Fe wt/wt ratio, but is also affected by the doses provided. When the Zn:Fe wt/wt ratio is kept constant we observed that at higher doses of both minerals (11.71 mg of Zn and 10 mg of Fe; Zn:Fe wt/wt ratio 1.17:1) Fe bioavailability was inhibited by 56%, while no inhibitory effect was observed at lower doses (0.59 mg of Zn and 0.5 mg of Fe; Zn:Fe wt/wt ratio 1.2:1) (Olivares et al. 2007b). In addition, we have shown that the inhibitory effect of Zn on Fe absorption is of short duration (Olivares et al. 2007c). Zn (11.71 mg) inhibited the absorption of 0.5 mg of Fe when both minerals were given simultaneously; however, when Zn was given 30 or 60 min before Fe no inhibitory effect was observed.

Effect of Zn added to foods on Fe absorption

Studies that have assessed simultaneously the effect of Zn fortification on Fe absorption are limited and conflicting results have been obtained when this interaction was studied in different food matrices (Table 2).

Table 1 Effect of Zn on Fe absorption: studies providing Fe and Zn as aqueous or saline solutions or as a supplement

References	Subjects	Fe absorption method	Zn and Fe compounds	Vehicle	Zn dose mg (μmol)	Fe dose mg (μmol)	Zn:Fe wt/wt ratio	Zn:Fe Molar ratio	Fe absorption[a]
Crofton et al. (1989)	9 adults	Area under plasma Fe increment time curve	$ZnSO_4$,	Water[c]	22.5 (344)	47.0 (842)	0.5:1	0.4:1	NE
	7 adults		$FeSO_4$		27.5 (421)	23.5 (421)	1.2:1	1.0:1	D
					68.5 (1,048)	23.5 (421)	2.9:1	2.5:1	D
Rossander-Hulten et al. (1991)	9 adults	Erythrocyte incorporation ^{55}Fe and ^{59}Fe	$ZnSO_4$,	Water	15.0 (229.5)	3.0 (53.7)	5:1	4.3:1	D
	10 adults		$FeSO_4$		45.0 (688.4)	3.0 (53.7)	15:1	12.8:1	D
Friel et al. (1998)	5 preterm infants	Erythrocyte incorporation ^{58}Fe	$ZnSO_4$,	Saline[d]	0.3 (4.6)[b]	0.3 (5.4)[b]	1:1		
			$FeCl_3$		1.2 (18.4)[b]	0.3 (5.4)[b]	4:1	3.4:1	D[e]
O'Brien et al. (1999)	28 pregnant women	Erythrocyte incorporation ^{57}Fe and ^{58}Fe	$ZnSO_4$,	Supplement	15 (229.5)	60 (1,074.4)	0.3:1	0.2:1	NE
			$FeSO_4$						
Olivares et al. (2007a)	22 adults	Erythrocyte incorporation ^{55}Fe and ^{59}Fe	$ZnSO_4$,	Water	0.29 (4.4)	0.5 (9.0)	0.6:1	0.5:1	NE
			$FeSO_4$		0.59 (9.0)	0.5 (9.0)	1.2:1	1.0:1	NE
					1.17 (17.9)	0.5 (9.0)	2.3:1	2.0:1	NE
					2.93 (44.8)	0.5 (9.0)	5.9:1	5.0:1	D
					5.80 (88.7)	0.5 (9.0)	11.6:1	10.0:1	D
					11.71 (179.1)	0.5 (9.0)	23.4:1	20.0:1	D
Olivares et al. (2007b)	14 adults	Erythrocyte incorporation ^{55}Fe and ^{59}Fe	$ZnSO_4$,	Water	0.59 (9.0)	0.5 (9.0)	1.2:1	1:1	NE
			$FeSO_4$		11.71 (179.1)	10.0 (179.1)	1.2:1	1:1	D
Olivares et al. (2007c)	14 adults	Erythrocyte incorporation ^{55}Fe and ^{59}Fe	$ZnSO_4$,	Water	11.71 (179.1)	0.5 (9.0)	23.4:1	20:1	D
			$FeSO_4$						

NE no effect, *D* decreased

[a] Compared with Fe alone

[b] mg (μmol)/kg

[c] Ascorbic acid (570 μmol) was included in the solution

[d] Infants received ascorbic acid (10 mg/kg)

[e] Compared to the absorption of low Zn dose

Table 2 Effect of Zn on Fe absorption: studies providing Fe and Zn in food matrices

References	Subjects	Fe absorption method	Zn and Fe compounds	Vehicle	Zn dose mg (μmol)	Fe dose mg (μmol)	Zn:Fe wt/wt ratio	Zn:Fe Molar ratio	Fe absorption[a]
Rossander-Hulten et al. (1991)	10 adults	Erythrocyte incorporation ^{55}Fe and ^{59}Fe	$ZnSO_4$, native no-heme Fe	Hamburger meal	15.0 (229.5)	3.0 (53.7)	5:1	4.3:1	NE
Friel et al. (1998)	9 preterm infants	Erythrocyte incorporation ^{58}Fe	$ZnSO_4$, $FeCl_3$	Premature formula or human milk[d]	0.3 (4.6)[b]	0.3 (5.4)[b]	1:1	0.9:1	
					1.2 (18.4)[b]	0.3 (5.4)[b]	4:1	3.4:1	NE[d]
Olivares et al. (2010)	15 adults	Erythrocyte incorporation ^{55}Fe and ^{59}Fe	Native Zn + $ZnSO_4$, native Fe + $FeSO_4$	Milk	1.66 (25.4)	2.0 (35.8)	0.8:1	0.7:1	NE
					2.66 (40.7)	2.0 (35.8)	1.3:1	1.1:1	NE
					4.66 (71.3)	2.0 (35.8)	2.3:1	2.0:1	NE
Bolívar et al. (2011)	13 adults	Erythrocyte incorporation ^{55}Fe and ^{59}Fe	Native Zn + $ZnSO_4$, native Fe + $FeSO_4$	Milk[c]	1.48 (22.6)	2.0 (35.8)	0.7:1	0.6:1	NE
					2.48 (37.9)	2.0 (35.8)	1.2:1	1.1:1	NE
					4.48 (68.5)	2.0 (35.8)	2.2:1	1.9:1	NE
Herman et al. (2002)	86 children	Erythrocyte incorporation ^{57}Fe and ^{58}Fe	$FeSO_4$ + ZnO	Wheat flour	1.5 (22.9)	1.5 (26.9)	1:1	0.9:1	NE
			$FeSO_4$ + $FeSO_4$		1.5 (22.9)	1.5 (26.9)	1:1	0.9:1	D
López de Romaña et al. (2005)	54 children	Erythrocyte incorporation ^{57}Fe and ^{58}Fe	$ZnSO_4$, $FeSO_4$	Wheat flour	3 (45.9)	3 (53.7)	1:1	0.9:1	NE
					9 (137.7)	3 (53.7)	3:1	2.6:1	NE
Olivares et al. (unpublished)	14 adults	Erythrocyte incorporation ^{55}Fe and ^{59}Fe	$ZnSO_4$, $FeSO_4$	Wheat flour	2.1 (32.1)	2.1 (37.6)	1:1	0.9:1	NE
					4.2 (64.2)	2.1 (37.6)	2:1	1.7:1	NE
					5.4 (82.6)	2.1 (37.6)	3:1	2.2:1	NE
Hettiarachchi et al. (2010)	30 children	Erythrocyte incorporation ^{57}Fe	ZnSO4, Fe fumarate	Ready-to-eat cereal	1.5 (22.9)	4.5 (80.6)	0.3:1	0.3:1	
					1.5 (22.9)	9.0 (161.2)	0.2:1	0:1:1	NE[e]

NE no effect, *D* decreased

[a] Compared with Fe alone

[b] mg (μmol)/Kg

[c] Milk fortified with ascorbic acid (molar ratio to Fe = 2:1)

[d] Compared to the absorption of low Zn dose

[e] Compared to the absorption of low Fe dose

Fe absorption was similar in ten adults receiving a composite hamburger meal (hamburger, green string beans, and mashed potatoes) containing 3 mg of native non-heme Fe, with or without 15 mg of Zn (11.1 ± 2.51 vs. 11.5 ± 2.27%) (Rossander-Hulten et al. 1991).

On the contrary to the results observed when either high (1,200 μg/kg) or low (300 μg/kg) doses of Zn were given in saline solution administered between feeds, Fe absorption was comparable in nine premature infants when Fe and Zn were provided with premature milk formula or human milk (Friel et al. 1998).We recently have shown that Zn does not significantly inhibit Fe absorption in 15 adult women who received 200 ml of milk (26% fat) fortified with 10 mg of Fe per liter of milk without and with graded concentrations of Zn (5, 10 and 20 mg/l) (Olivares et al. 2010). A similar result was obtained when this study was repeated in 13 women using the same study design, but where milk was also enriched with 70 mg of ascorbic acid per liter of milk (Bolívar et al. 2011).

Studies performed providing wheat flour co-fortified with Zn and Fe have yielded conflicting results. Fe absorption was measured in 86 children (4–6 years old) randomly assigned to consume wheat flour dumplings containing 25 g flour fortified with either 60 mg Fe/kg alone or with the same amount of Fe and 60 mg Zn/kg as zinc oxide or as zinc sulfate (Herman et al. 2002). Fe absorption was significantly lower from the flour co-fortified with zinc sulfate, but not from the flour co-fortified with zinc oxide, which is much less soluble in water than is zinc sulfate. Fe absorption of flour fortified with Fe, Fe plus ZnO and Fe plus $ZnSO_4$ was 15.9 ± 6.8, 14.0 ± 8.9 and 11.5 ± 4.9%, respectively. On the other hand, Zn absorption was not significantly different between the zinc oxide and zinc sulfate co-fortified flours. López de Romaña et al. (2005) found no detrimental effect of Zn on Fe absorption in 54 anemic children (3–4 years old) randomly assigned to receive at breakfast and lunch, 100 g wheat products fortified with either 30 mg/kg Fe alone or Fe plus 30 or 90 mg of Zn/kg flour.

We recently found no statistically significant differences in Fe absorption in 14 adult women receiving 100 g of bread prepared with 70 g of refined wheat flour that was fortified with 30 mg of Fe/kg, as ferrous sulfate, alone or with 30, 60 or 90 mg/kg of Zn as $ZnSO_4$ (Olivares et al. unpublished observations).

The absorption of Fe of 50 g of a precooked ready-to-eat cereal based food (maize flour, soya powder, milk powder, and vitamin–mineral premix) was measured, by erythrocyte incorporation of ^{57}Fe, in children 4–7 years old (Hettiarachchi et al. 2010). The meal was fortified with 1.5 mg of Zn, as zinc sulfate and either 9 mg or 4.5 mg of Fe, as ferrous fumarate. No differences in Fe absorption were found between children receiving the high Fe concentration (6.6%, range ± 1 SD 4–8; $n = 15$) and the low Fe concentration (4.8%, range ± 1 SD 2–6; $n = 15$).

Discussion and conclusions

The reviewed studies contribute to the knowledge of the interactions between Zn and Fe provided as either aqueous or saline solutions, medicinal supplements or fortified foods, and provide clues to understanding the mechanisms of the interactions between Zn and Fe. These results are useful for supplementation or fortification programs using both minerals.

The ratio of Zn:Fe that inhibits absorption depends on the concentration given of both cations and the vehicle in which both elements are administered. The amount of ionic species available for uptake by the enterocyte is higher when these minerals are given in aqueous or saline solutions. On the contrary, when Zn and Fe are added to a food they interact with dietary ligands that decrease the number of available cations competing for transport at the enterocyte. It has been speculated that the mutual negative interaction between Fe and Zn is due to a competitive binding to DMT1, the main non-heme Fe transporter, which participates in the transport of a variety of divalent metals including Zn (Gunshin et al. 1997; Garrick et al. 2003). However, there has been debate over the physiological role of the transporter DMT1 in cellular Zn uptake (Kordas and Stoltzfus 2004; Tallkvist et al. 2000; Garrick et al. 2006), and there is evidence that Zn uptake is not affected by reduced expression of DMT1 Tandy et al. (2000). Furthermore, whereas DMT1-mediated transport is coupled to proton co-transport; uptake of Zn by small intestinal brush border membrane vesicles is inhibited by an inflow directed proton gradient (Tacnet et al. 1993).

The different pattern of response of the inhibitory effect of Zn on Fe absorption observed when lower or higher doses of Zn and Fe are provided could be

explained by the difference in the abundance of both cations as they compete for a limited number of shared transporters at the enterocyte. At higher doses of both minerals all shared transporters molecules are occupied and the inhibitory effect of Zn on Fe absorption can be observed even at a Zn-to-Fe wt/wt ratio of 1:1. Alternatively, at low doses of Fe, shared transporters remain available until the Zn-to-Fe wt/wt ratio reaches a value $\geq$5.9. We have shown in Caco-2 cells that knock-down of DMT1 reduces but not abolishes Fe uptake (Espinoza et al. 2011, demonstrating the existence of other pathways of Fe uptake. We have also found that knock-down of CTR1 decreases Fe and Zn uptake (Arredondo et al. 2006). It has been postulated that there is a common pathway of Fe and Zn uptake, different from the DMT1, located in the apical membrane of the intestinal cell (Yamaji et al. 2001; Abd Rashed 2011). On the other hand, evidence obtained from kinetic studies of Fe and Zn uptake performed in Caco-2 cells supports the existence of a dual Fe transport mechanism involving DMT1 and another Fe transporter, and that the inhibition of Zn on Fe uptake occurs by a non-competitive inhibition (Iyengar et al. 2009, 2010).

The finding that the inhibitory effect of Zn on Fe absorption, in aqueous solution, occurs at Zn:Fe wt/wt ratio of 1:1, while the negative effect of Fe on Zn absorption is seen at a Fe:Zn wt/wt ratio >2:1, it is not fully explained by a competition for DMT1 transport because this transporter has a greater affinity for Fe than for Zn (Garrick et al. 2003, 2006).

Given that in most of the reviewed studies Fe bioavailability was measured (Fe utilization for hemoglobin production) rather than Fe absorption, it is not possible discard that in addition of the negative interaction between Fe and Zn at the absorptive level, both minerals could negatively interact at the plasmatic transport or tissue utilization level. It has been shown that transferrin, the main Fe plasma transporter, can also bind Zn (Harris 1983). Furthermore, it appears that Zn is able to block the Fe storage capacity of ferritin (Harrison 1996; Niereder 1990). More recently, it has been demonstrated that the Zn transporter Zip14 mediates non-transferrin-bound Fe uptake into hepatocytes (Liuzzi et al. 2006) and transferrin Fe uptake in HepG2 cells (Zhao et al. 2010), thus it is possible speculate that non-transferrin and transferrin Fe uptake by erythrocyte progenitors may be compromised.

The finding from a few long term studies showing that the combined supplementation with Fe and Zn was less effective than single supplementation with Fe in improving Fe status (Dijkhuizen et al. 2001; Lind et al. 2003; Schultink et al. 1997) may be attributed to the inhibitory effect of Zn on Fe bioavailability; however, other studies have not confirmed the unfavorable effect of combined supplementation with both elements (Fischer-Walker et al. 2005), and three studies performed in subjects presumably Fe and Zn deficient found a higher increase of hemoglobin after combined Fe and Zn supplementation than with either Fe or Zn supplementation alone (Nishiyama et al. 1996, 1998, 1999). This discrepancy may be partially explained by differences in the Zn to Fe ratio of the supplements and/or differences on the prior Fe and Zn status of the subjects.

It can be concluded that: (1) The inhibitory effect of Zn on Fe absorption, in aqueous solution, occurs at Zn:Fe wt/wt ratio of 1:1, while this negative effect is not observed in food matrixes. However, a decrease in Fe absorption was observed in only 1 of 3 studies when Fe and Zn were supplied in wheat flour. (2) The knowledge of the mutual negative interaction between Zn and Fe in supplements and fortified foods should be considered in the design of supplementation or fortification programs with both elements. (3) Further research is needed to understand the mechanism of interaction between Fe and Zn. Questions that remain to be answered include: inhibition competitive or not competitive? What is the role of DMT1 and other transporters? What is the influence of prior Fe and Zn status?

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