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Iron–zinc and calcium–Fe interactions in relation to Zn and Fe absorption

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Fe deficiency is the most common nutritional deficiency disorder in the world, thus measures are taken to improve Fe nutrition by introducing additional Fe into the diet, either by fortification of foods, such as commercial infant foods or by taking Fe supplements. A number of dietary factors have been shown to promote or reduce the absorption of Zn (Fairweather-Tait, 1988) and Fe (Hallberg, 1981), including the presence of other inorganic elements. Although the adverse effect of Fe on Zn absorption is well documented (Solomons, 1988), there is still some uncertainty about the long-term effects of fortification and/or supplemental Fe on Zn nutrition.

High intakes of Ca are recommended, particularly from 11–24 years of age (National Research Council, 1989), in order to obtain peak bone mass and, thus, prevent or delay osteoporosis. Ca can be obtained from high-Ca foods such as milk and milk products, water, and/or Ca supplements. Recently there has been a marketing drive in the USA to promote indigestion remedies containing CaCO₃ as a dietary Ca supplement. Since Ca has been shown to adversely affect Fe absorption, a suggestion has been made that the intake of dairy products should be reduced with the main Fe-containing meals (Hallberg *et al.* 1992a).

The present paper will briefly review and critically evaluate what is currently known about Fe–Zn and Ca–Fe interactions and their potential effects on health.

POSSIBLE MECHANISMS OF ACTION

Hill & Matrone (1970) first proposed that elements with similar physical and chemical properties act antagonistically to each other in biological systems. They suggested that the electronic configuration of the element can be used to predict possible interactions. However, there are also some interactions between elements that do not share common electronic structures of valence shells. As yet the mechanisms whereby Fe and Ca reduce Zn and Fe absorption respectively are not yet fully understood (Mills, 1985; Solomons, 1988; Hallberg *et al.* 1992b).

Important mineral–mineral interactions can occur anywhere in the food chain, as illustrated in Table 1. Most of the important interactions occur in the gastrointestinal tract, probably through one of the following mechanisms.

Table 1. *Stages in the food chain where mineral–mineral interactions can occur*

Site of effect	Type of interaction
Geochemical	Soil–water–plant–animal chain
Food and/or drinks	Processing effects
Gastrointestinal tract	Lumen interactions and/or excretion
Absorptive mucosal cells	Serosal transport and/or excretion in sloughed cells
Blood	Transport and/or glomerular filtration
Tissues	Functional proteins and/or enzymes and/or storage sites

Competition for mineral-binding ligands

Interactions may occur in the intestinal lumen, as reported for Fe and Zn (Rossander-Hulten *et al.* 1991). A large number of dietary constituents have been identified *in vitro* as binding minerals at the appropriate pH, and many of these have been shown *in vivo* to exert an effect on absorption, for example ascorbic acid and phytate. When these substances are limiting (i.e. there is an excess of minerals), only a limited quantity of each mineral can be bound to the ligands. The relative distribution of the minerals will depend upon the binding constants, thus, in theory, less Fe will be bound to phytate in the presence of high concentrations of Zn, and hence more should be available for absorption. Synergism may occur between ligands and minerals, producing complexes, as for example occurs with Zn, Ca and phytate (Mills, 1985). Ligands may exert opposite effects on different minerals, for example ascorbic acid enhances Fe but reduces Zn absorption (Fairweather-Tait, 1988).

Competition for uptake

Chemically-similar elements may share common pathways for absorption, thus the co-ingestion of two or more elements will result in competition for uptake into the mucosal cells. This mechanism has been proposed for Zn–Fe interactions (Aggett *et al.* 1983; Solomons, 1986).

Co-adaptation

Rosenberg & Solomons (1984) suggested that the dietary intake of one mineral may introduce intracellular transfer or mucosal trapping mechanisms that then influence the absorption of another mineral. This co-adaptation derives from a direct intracellular action by a mineral or by some hormonal signal reflecting its tissue stores. Deficiency or sufficiency of one mineral, therefore, can determine the absorptive efficiency of another. Fe deficiency has been the proposed mechanism for the increased uptake of other inorganic elements such as Cd (Mills, 1985) and Zn in rats (Flanagan *et al.* 1980), but an increased efficiency of absorption of Fe *per se* is not paralleled by an increase in Zn absorption (Valberg *et al.* 1984).

Effects on physiological variables

The intake of a mineral might have a direct effect on gastrointestinal conditions which then have an influence on the absorption of another mineral. For example, high oral

Table 2. *Effects of iron on zinc absorption in human subjects*

Zn (mg)	Fe (mg)	Test meal	Effect	Reference
25	25	Coca-Cola®	0/↓	Solomons & Jacob (1981)
25	75		↓	
25	75	Haem-Fe	0	
54	100	Oysters	0	
22.5	47	Water	↓	Aggett <i>et al.</i> (1983)
6.0	51.5	Water	↓	Valberg <i>et al.</i> (1984)
6.2	26.9	Haem-Fe	↓	
4.0	17.1	Turkey	0	
2.6	2.2	Water	0	Sandstrom <i>et al.</i> (1985)
	5.6		0	
	56.0		↓	
	2.2	Meal	0	
	5.6		0	
	56.0		0	
1.87 mg/l	2.5 mg/l	Infant formula	0	Haschke <i>et al.</i> (1986)
1.88	10.5		0	
0.44	10.0	Wheat-flour cereal	0	L. Davidsson (personal communication)
0.44	25.0		0	
0.51	4.5	White bread	0	
0.50	5.5	Infant formula	0	
0.60	6.6	Weaning food	0	S. J. Fairweather-Tait, S. G. Wharf and T. E. Fox (unpublished results)

0, No effect; ↓, absorption decreased; 0/↓, both effects observed.

doses of CaCO₃ might produce rebound gastric hyperacidity and, therefore, might promote the absorption of non-haem-Fe (Solomons, 1988), because acid conditions favour Fe solubilization from food.

IRON-ZINC INTERACTIONS

A number of papers have been published describing the effects of Fe on Zn absorption, as summarized in Table 2. Although the results are conflicting, the negative effect of Fe on Zn reported in some of the studies has stimulated concern over the possible adverse effects of fortifying foods with Fe, as well as the practice of taking Fe supplements, on Zn nutrition. One of the main problems with research into Zn metabolism is the lack of suitable and sensitive indices of body Zn levels. Dawson *et al.* (1989) found that Fe supplementation resulted in lower serum Zn concentrations in pregnant teenagers, but since serum or plasma Zn concentrations are not considered to be a good index of body Zn levels, no conclusions can be made regarding the effect of Fe supplements on Zn status *per se*. However, the results could reflect a redistribution of Zn within the body as a result of taking additional Fe.

Studies of Fe-Zn interactions usually employ the technique of measuring Zn absorption in the presence of differing levels of Fe in test meals or oral doses in order to assess the possible effect of Fe on Zn nutrition. A very important aspect of Zn metabolism that

should not be forgotten is the ability of the body to alter Zn excretion and efficiency of absorption in order to maintain Zn homeostasis under different dietary conditions (Jackson, 1989). Therefore, over longer periods of time, adaptive mechanisms may well compensate for adverse effects of Fe on Zn absorption from single test meals.

In the early human studies pharmacological doses of Zn were given and plasma Zn response curves used to assess the effect of Fe on Zn absorption (Solomons & Jacob, 1981; Aggett *et al.* 1983; Meadows *et al.* 1983; Solomons *et al.* 1983). Using this technique, doses of Fe as low as 12.5 mg were shown to significantly reduce Zn absorption from 12.5 mg Zn. There are acknowledged limitations to this particular method, however, in that plasma curves do not reflect net uptake of Zn and the test dose of Zn is much higher than normal dietary Zn intake. In his review of the interaction between Fe and Zn, Solomons (1986) concludes that the total amount of ionic species determines the effect on absorption of Zn. He suggests that a total single dose greater than 25 mg will produce a measurable effect on human Zn nutrition. Animal studies in which dose-response measurements have been made also indicate that the threshold level for an effect of Fe on Zn absorption depends on the total ionic (Fe plus Zn) species present in the test meals (Fairweather-Tait & Southon, 1989).

Most studies on Fe-Zn interactions have been carried out using different levels of the two minerals administered simultaneously. When Meadows *et al.* (1983) investigated the duration of the effect of Fe by giving adults daily tablets containing Fe (100 mg) and folic acid (350 µg), as often prescribed for pregnant women, for 14 d, they found a reduction in Zn absorption. The plasma concentration time curve response following an oral dose of 50 mg Zn was measured before and 24 h after the period of Fe supplementation. There was a significantly reduced area under the curve after 14 d supplementation. Various explanations were proposed, including inter-element competition in the intestine and reduced binding of Zn to plasma proteins. The latter suggestion was considered unlikely because an increase in systemic clearance would have resulted in a faster elimination rate-constant, but the opposite, in fact, was observed. Thus, the authors concluded that the increased concentration of Fe in the mucosal cells following a period of supplementation displayed a larger mass of Zn, hence delaying its absorption. When, however, this hypothesis was carefully tested in rats, previous feeding with a high-Fe diet was not found to affect subsequent absorption of Zn (Fairweather-Tait & Southon, 1989). Furthermore, Solomons *et al.* (1983) did not find a reduction in Zn uptake into plasma from a 25 mg dose of Zn taken alone after Fe supplementation of healthy volunteers (130 mg/d for 4 d). The difference in the results between the studies may possibly be explained by the more intensive and prolonged treatment in the investigation of Meadows *et al.* (1983).

Studies using doses in a more physiological range can be performed using isotopes (radio- or stable) of Zn. Sandstrom *et al.* (1985) gave 2.6 mg Zn labelled with ⁶⁵Zn together with varying levels of Fe (0, 2.2, 5.6 and 56.0 mg) to adult volunteers and measured ⁶⁵Zn retention by whole-body counting. The Fe:Zn molar ratio was shown to be an important determinant of Fe-Zn interactions. A significant reduction in Zn absorption from Zn solution in water was observed when Fe:Zn was 25:1 (2.6 mg Zn plus 56 mg Fe), but there was no effect at ratios of 2.5:1 and 1:1. However, when the Zn and Fe were given with a meal of rice with meat sauce, the inhibitory effect was no longer seen. Two recent studies in which the effects of Fe fortification of infant foods was examined using Zn isotopes in infants (S. J. Fairweather-Tait, S. G. Wharf and T. E.

Fox, unpublished results), and adults (Davidsson *et al.* 1995) have both demonstrated no effect of Fe (at the levels usually added to infant foods) on Zn absorption from naturally-occurring Zn (see Table 2).

CALCIUM-IRON INTERACTIONS

The conclusion drawn from early balance studies investigating Ca-Fe interactions in humans was that Ca has a beneficial effect on Fe absorption (Apte & Venkatachalam, 1964); this contrasted with results from rat studies (Davis, 1959). The apparent anomaly between animals and man may be explained by examining the composition of the diets fed to the human subjects. With high levels of phytate (>400 mg phytate-P/d), as used by Apte & Venkatachalam (1964) in their typical Indian diets, additional Ca in the diet (>600 mg/d) may actually have enhanced Fe absorption because it was bound preferentially by phytate, thereby leaving more Fe free to be taken up by the intestinal mucosal cells. Although chemical balance studies of inorganic nutrients are extremely difficult to perform accurately, the work of Apte & Venkatachalam (1964) is a good illustration of the importance of taking the composition of the whole diet into consideration when evaluating the effect of one nutrient on another. Recent work by Hallberg *et al.* (1992a) using Fe radio-isotopes confirmed the Ca-Fe-phytate effect. They found that the inhibitory effect of added Ca (300 mg per meal) to wheat rolls was reduced in the presence of phytate (25 mg phytate-P per meal).

The results of animal studies in which large amounts of Ca salts had been reported to interfere with Fe absorption prompted Mosen & Cook (1976) to study the effects of physiological levels of Ca (approximately 200 mg per meal) and phosphate (approximately 400 mg P per meal) on the absorption of ^{55}Fe and ^{59}Fe (4.1 mg per meal) from a semi-synthetic meal in adult volunteers. Fe absorption was determined by measuring haemoglobin incorporation of the Fe isotopes 14 d after the test meals. With the single addition of Ca or phosphate to the test meals, no significant inhibitory effect was seen. However, the combined addition of Ca and phosphate resulted in a significant reduction in Fe absorption, and the suggestion was made that a Ca-phosphate-Fe complex was formed, thereby inhibiting Fe absorption. Results of a later chemical balance study by Snedeker *et al.* (1982) do not agree with the single-meal challenge of Mosen & Cook (1976). Subjects were fed on moderate-Ca-moderate-P, moderate-Ca-high-P and high-Ca-high-P diets for 12 d periods. The moderate- and high-Ca diets contained 780 and 2382 mg Ca respectively. The moderate- and high-P diets contained 843 and 2442 mg P respectively. Fe intakes averaged 17.5 mg/d. There were no significant differences in Fe retention between the three dietary periods, nor were plasma ferritin levels affected by the dietary treatment.

In recent years there has been increasing concern about the possible adverse effects of Ca on Fe absorption, primarily because of current dietary advice to increase Ca intakes in women in order to reduce the risk of osteoporosis. Bearing in mind the relatively high prevalence of Fe deficiency in women, and the unresolved controversy about supplementing the diet with Ca (Kanis & Passmore, 1989a,b; Nordin & Heaney, 1990), it is important to have a clear understanding of the interrelationship between Ca and Fe.

The effect of Ca supplements taken with meals has been addressed in a number of studies (Table 3). Cook *et al.* (1991) found that CaCO_3 , calcium citrate and $\text{Ca}_3(\text{PO}_4)_2$ (600 mg Ca) reduced non-haem-Fe absorption from a hamburger meal. Calcium citrate

Table 3. *Effect of calcium supplements on iron absorption*

Supplement	Test meal	Effect	Reference
CaCO ₃ (600 mg Ca)	18 mg Fe	0	Cook <i>et al.</i> (1991)
Calcium citrate or calcium phosphate		↓	
CaCO ₃ , calcium citrate or calcium phosphate	5.1 mg Fe (meal)	↓	
CaCO ₃ (500 mg Ca)	3.6 mg Fe (meal)	↓	Dawson-Hughes <i>et al.</i> (1986)
Hydroxyapatite (500 mg Ca)		↓	
CaCl ₂ (3 mg Ca)	0.01 mg Fe	0	Hallberg <i>et al.</i> (1992a)
CaCl ₂ (165 mg Ca)	3.8 mg Fe (meal)	↓	Hallberg <i>et al.</i> (1992b)
CaCl ₂ (40–600 mg Ca)	3.5 mg Fe (wheat rolls)	↓	Hallberg <i>et al.</i> (1991)
Ca-citrate-malate (500 mg Ca)	3.2 mg Fe (meal)	↓	Deehr <i>et al.</i> (1990)

0, No effect; ↓, absorption decreased.

and Ca₃(PO₄)₂, but not CaCO₃, reduced Fe absorption from FeSO₄ (18 mg Fe). At lower doses of Ca (300 mg) and higher Fe (37 mg) no effect was seen. A similar effect was observed by Dawson-Hughes *et al.* (1986) who gave a breakfast meal containing 3.6 mg Fe, extrinsically labelled with ⁵⁹Fe, both with and without 500 mg Ca. CaCO₃ and hydroxyapatite significantly reduced Fe retention, as measured by whole-body counting. Ca has a direct dose-related inhibiting effect on Fe absorption; Hallberg *et al.* (1991) showed that there was a continuous decrease in absorption of Fe with increasing dose of Ca (from 40–300 mg), and within the range of 300–600 mg the reduction was 75–80%. No duration of the effect of Ca on non-haem-Fe has been observed in human subjects (Gleerup *et al.* 1993).

An inhibitory effect of Ca has been reported also with haem-Fe (Hallberg *et al.* 1992b). The mechanism for this is unclear. The authors have proposed that the effect is related to mucosal transfer of Fe, a stage that is common for haem- and non-haem-Fe. An alternative explanation could be that some of the haem-Fe is degraded in the gastrointestinal tract and that the liberated Fe from haem then participates in interactions in the lumen with Ca. Previous exposure of the intestinal mucosal cells to Fe has an effect on the subsequent efficiency of absorption of Fe, but not of Ca (Gleerup *et al.* 1993; Fairweather-Tait & Minihane, unpublished results), suggesting that the Ca-Fe interaction occurs only in the lumen. Further work is required to elucidate the mechanism(s) involved.

Ca-rich foods have been shown also to reduce Fe absorption, although there are conflicting reports in the literature (for review, see Jackson & Lee, 1992), probably related to differences in the technique used to assess the effects of Ca on Fe bioavailability. Hallberg's group (Rossander *et al.* 1979) demonstrated no adverse effect of consuming milk with cereal (cornflakes) on Fe absorption from a breakfast meal of rolls and coffee. Turnlund *et al.* (1990) showed no significant effect of milk on Fe absorption in women from the whole diet (8.04% without milk and 8.97% with milk, pooled SEM 0.37%). Conversely, Deehr *et al.* (1990) found that Fe absorption from a breakfast meal containing 3.2 mg Fe was 8.3 (SEM 4.6) % but when consumed with 450 ml

whole milk (446 mg Ca), absorption fell to 3.4 (SEM 3.4) %, and the addition of cheese (650 mg Ca) to pizza (4.3 mg Fe), and milk (230 mg Ca) or milkshake (395 mg Ca) to a hamburger meal (3.9–4.4 mg Fe) significantly reduced non-haem-Fe absorption (Hallberg *et al.* 1992a).

Although Ca has been shown in many instances to reduce Fe absorption from meals, the most important end-point is the effect of the Ca–Fe interaction on body Fe levels. Sokoll & Dawson-Hughes (1992) found no significant effect of taking 500 mg Ca (as CaCO₃) with two meals daily for 12 weeks on plasma ferritin concentrations of free-living premenopausal women. Mean baseline plasma ferritin concentrations ($\mu\text{g/l}$) were 47.2 (SD 42.3) in the control group and 34.9 (SD 27.6) in the treatment group. After 12 weeks the control group rose by 2.6 (SD 39.7) % and the treatment group fell by 2.2 (SD 38.4) %. Prentice *et al.* (1993) also reported no change in plasma ferritin concentrations in lactating women taking 1000 mg Ca (as CaCO₃) 5 d per week for 12 months, but this was between meals, thus unlikely to reduce Fe absorption from the meals. Further work is required on the long-term effect of taking Ca supplements and dairy foods with meals on body Fe stores.

CONCLUSIONS

Fe–Zn interactions in the diet are only important when the total ionic species in any one meal exceeds 25 mg (Solomons, 1986). This situation may occur with Fe supplements when they are taken with meals, but as this will result in lower Fe absorption the advice is usually to take Fe between meals. Fortifying foods with Fe is not likely to affect Zn absorption. Recent studies investigating infant formula and weaning foods have shown no adverse effects of added Fe on Zn absorption.

The adverse effects of Ca on Fe absorption from single test meals has led to the recommendation by Hallberg's group (Hallberg *et al.* 1992a) 'to reduce the intake of dairy products with the main meals providing most of the dietary iron, especially for those having the highest iron requirements i.e. children, teenagers and women at childbearing age', and this group has recently observed a higher absorption of Fe from mid-day and evening meals when no milk or cheese was served with the meals (Gleerup *et al.* 1995). Yet Jackson & Lee (1992) conclude that 'the nutritional benefits provided by dairy products outweigh the slight inhibitory effect they may have on iron availability'. The real questions that need to be addressed are (a) whether or not Ca in the diet (in dairy foods or as supplements) has an adverse effect on body Fe levels, not just on Fe absorption from test meals, and (b) the relative importance in the population of nutritional problems relating to Ca and Fe. There is some indication that Ca supplements do not reduce Fe stores, assessed by plasma ferritin concentrations (Sokoll & Dawson-Hughes, 1992; Prentice *et al.* 1993), but further research on this important issue is required.

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