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Calcium and Iron Absorption – Mechanisms and Public Health Relevance

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Abstract: Studies on human subjects have shown that calcium (Ca) can inhibit iron (Fe) absorption, regardless of whether it is given as Ca salts or in dairy products. This has caused concern as increased Ca intake commonly is recommended for children and women, the same populations that are at risk of Fe deficiency. However, a thorough review of studies on humans in which Ca intake was substantially increased for long periods shows no changes in hematological measures or indicators of iron status. Thus, the inhibitory effect may be of short duration and there also may be compensatory mechanisms. The interaction between Ca and Fe may be a lumenal event, affecting Fe uptake through DMT1 (divalent metal transporter 1) at the apical membrane. However, it is also possible that inhibition occurs during Fe transfer into circulation, suggesting roles for the serosal exporter ferroportin (FPN) and hephaestin. We explored these possibilities in human intestinal Caco-2 cells cultured in monolayers. Iron transport (^{59}Fe) and expression of DMT1, FPN, and hephaestin were assessed after 1.5 and 4 hours with 0 or 100 μM $CaCl_2$. Although Ca did not affect Fe uptake or DMT1 expression at 1.5 hours, FPN abundance at the basolateral membrane decreased, resulting in increased cellular Fe retention and decreased Fe efflux. After 4 hours, DMT1 and FPN expression increased and there was increased FPN at the membrane, suggesting a rebound effect. Thus, the effect of Ca on Fe absorption may be of short duration and adaptation may occur with time. This may explain why studies on long-term Ca supplementation of different groups fail to show any adverse effects on Fe status.

Introduction

The adverse effects of iron deficiency anemia and iron deficiency are well known and interventions using iron fortification or supplements have been implemented to prevent iron deficiency. However, even if such strategies may be successful in part, it is evident that a common problem is the presence of dietary factors, such as phytate and polyphenols, which inhibit iron absorption. Any approach to improve iron status of vulnerable populations should therefore include the consideration of limiting the intake of such inhibitory factors.

Calcium has been found to have a negative effect on iron absorption in humans [1–6]. Over a range of "physiological" calcium intakes, iron absorption was inversely correlated to the calcium content of the meal (5). Similar effects were observed for calcium salts (used for supplements) and milk/dairy products. An apparent solution to this nutritional problem would be to limit the calcium content of iron-containing meals so that iron absorption is optimized [7]. However, this strategy leads to concern

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about calcium nutrition. It is well known that the same population groups that are vulnerable to iron deficiency; i. e., infants, children, and women of childbearing age, also have high requirements for calcium. Indeed, the most recent DRIs [Dietary Reference Intakes] for calcium were increased as a consequence of findings on the health benefits of high calcium intake [8]. Restricting the calcium content of one or two of the major meals of the day creates considerable difficulties to achieve the recommended daily intakes of calcium. For example, a young teenage girl who is recommended to consume 1000 mg of calcium per day, may normally take this in during three meals (breakfast, lunch, dinner) and a sizeable snack, which translates to an average of 250 mg per meal. If two of these meals are supposed to be low in calcium (to improve iron absorption), the other two meals need to contain 500 mg per meal. This is difficult to achieve with "normal" food components and will most likely necessitate calcium fortification and/or calcium supplementation. This, in turn, will require an awareness of the consumer to a) select high-calcium diets for some meals and b) to select iron-containing foods at certain meals, while limiting calcium intake from the same meals. From a health education point of view, this is a complex and difficult message to convey. Before attempting to revise dietary guidelines and their implementations (school lunch programs, food provisions, etc.), it appears reasonable to explore whether acute effects of calcium or iron absorption cause any negative long-term effects on iron status.

A critical evaluation of studies showing an acute effect of calcium on iron absorption

Taken together, most studies on the effects of calcium on iron absorption show that an inhibition does occur. However, most of the studies showing this effect used the same basic methodology; i. e., single meals, dual radioisotope labeling, and red blood cell iron incorporation. Some aspects of this method have been questioned and the possibility that it exaggerates the effect of dietary factors on iron absorption has been raised.

Monsen and Cook [1], using the dual radioisotope method and single meals, showed that iron absorption was reduced by 70 % when 180 mg of calcium was added to a semi-synthetic meal when meat was absent, and by 50 % when meat was present. In contrast to several other studies, however, the negative effect of calcium was only observed when phosphate was given with the calcium; no effect was observed for calcium alone. The reason for the discrepancy between this study and more recent studies using similar methods is not known. Dawson-Hughes *et al.* [2], using a single radioisotope in a crossover, single-meal study of postmenopausal women, found that 500 mg of calcium given as calcium carbonate or hydroxyapatite reduced iron absorption by 57 % and 54 %, respectively, as compared to a low-calcium meal. Deehr *et al.* [3] used the single radioisotope method and a crossover design in postmenopausal women and found that iron absorption was decreased by 60 % when calcium (238 mg) was added in the form of milk, by 30 % when added as calcium citrate-malate to water, and insignificantly (11 %) when added as calcium citrate-malate to orange juice. This study suggested that the form of calcium presented may influence the calcium effect. Hallberg *et al.* [5] also found that calcium inhibited iron absorption using the dual radioisotope method; human adults given single meals with 40–600 mg calcium showed a dose-dependent decrease in iron absorption by 50–60 %, regardless of the form of calcium given ($CaCl_2$, milk calcium, or cheese calcium). Heme iron absorption was also significantly decreased (24 % vs. 49 % for "control" meals). Recently, Benkhedda *et al.* also showed that calcium (500 mg as carbonate) reduced iron absorption from a single meal from 10.2 % to 4.8 % [9], but the magnitude of the calcium effect varied considerably among subjects. These authors had selected women with marginal iron status in order to minimize the large inter-individual variation in iron absorption found in most studies. However, even in these subjects with a very narrow range of iron stores (serum ferritin), iron absorption was highly variable and they concluded that factors other than individual iron status are responsible for this variation. It is possible that the expression of iron transporters responsible for intestinal absorption of iron and their cellular localization may be affected by several factors other than iron status (see below).

That the composition of the meal to which calcium is added may affect the extent of the inhibition on iron absorption observed was investigated by Cook *et al.* [4]. They found that calcium given as carbonate or phosphate showed some inhibitory effect on iron absorption when added to meals with enhancers of iron absorption present (e. g., ascorbic acid) and that calcium citrate had no effect, while all three forms of calcium had a highly negative effect on iron absorption when they were added to a meal with inhibitors of iron absorption (e. g., phytate) present. A variation of the single-meal method was investigated by Cook

et al. [10]. In this design, two meals per day over a two-week period were labeled with radio iron and the effects of enhancers and inhibitors on iron absorption were investigated when subjects consumed self-selected diets as compared to pre-designed meals. When subjects consumed the self-selected diets (usually containing low/moderate amounts of both inhibitors and enhancers), there was good agreement between the single-meal method and the absorption from the entire diet, while this was not the case for diets containing either enhancers or inhibitors. The enhancing/inhibitory effects were considerably less pronounced when self-selected meals were consumed and a plausible explanation given by the authors for the difference between single-meal and whole-diet results was that "the influence of dietary inhibitors and enhancers is diluted in a normal diet by meals that have no overall effect on non-heme iron absorption." The authors concluded that this "meal composition" effect should be considered when single-meal studies are performed.

The "timing" of the calcium effect on iron absorption was studied by Gleerup *et al.* [11]. Using the dual radioisotope method, they found that the negative effect of calcium (340 mg) was not observed if it was given in a breakfast meal 2 or 4 hours prior to a lunch meal containing the iron radioisotope, suggesting that calcium needs to be present at the same time as iron absorption when the meal in question occurs.

The possibility of the methodology used influencing the effect of calcium observed has been raised in several studies. An early balance study by Snedeker *et al.* [12] in which a moderate-calcium (780 mg/day) or a high-calcium diet (2382 mg/day) was fed to human volunteers for 39 days showed no significant difference in daily fecal iron excretion, suggesting that regulation of iron absorption occurs after some time. Tidehag *et al.* [13] used ileostomy subjects and self-selected diets with a low calcium and phytate content during an eight-week study period, and found no significant effect on iron absorption as determined from the ileostomy bags when calcium was added in the form of milk, fermented milk, or as soft drinks. Gleerup *et al.* [7] modified the design of their dual radioisotope method so that all meals were extrinsically labeled with radio iron for a two-week period, and a high-calcium diet (937 mg/day) was provided either at lunch and dinner for a one -week period or at the breakfast and an evening meal for the alternative two-week period. A significant negative effect on iron absorption was found, but it was now 30–35 % lower as compared to 50–65 % in their previous study [5], suggesting that the magnitude of the effect depends on the design of the experiment. Reddy and Cook [14] labeled two main meals per day (69–78 % of daily iron) with radio iron for five-day periods and studied the effect of varying the daily calcium intake from 280 to 1281 mg in self-selected diets. Iron absorption was 5.01 %, 4.71 %, and 5.83 %, respectively, from the low-, normal-, and high-calcium diets; these results were not significantly different. The authors concluded that calcium intake has no significant influence on non-heme iron absorption from a varied diet and stated that "the relevance of single-meal studies in estimating the major determinants of food iron availability from a complete diet is debatable." Roughead *et al.* [15] used single meals with a whole gut-lavage method and whole-body counting and found that calcium supplementation reduced heme-iron absorption and total iron absorption without significantly affecting non-heme iron absorption. "Initial mucosal uptake" was estimated from isotope retention at 8 hours post-meal, but this time period may possibly include both an initial decrease and a possible compensatory increase (see discussion below). It should also be noted that the magnitude of calcium inhibition was similar for the two forms of iron: a non-significant/marginally significant inhibition of 20–25 % for non-heme iron and a significant inhibition of 27 % for heme-iron absorption. The difference between a significant and non-significant effect may therefore be due to differences in inter-individual variation for the two forms, or a matter of power of the study.

Using another approach, Tidehag *et al.* [16] fed ileostomy subjects either a high- or a low-fiber diet for five consecutive days. On days 4 and 5, the morning meal was labeled with one radioisotope of iron (^{55}Fe) and all three major meals labeled with another one (^{59}Fe). Iron absorption was found to be 80 % higher from the low-fiber meal when single meals were labeled as compared to all meals, and for the high-fiber diet iron absorption was 50 % lower when single meals were used as compared to whole diets. These results clearly demonstrate that the single-meal method exaggerates the effects of enhancers/inhibitors on iron absorption. This is supported by the observations of Grinder-Pedersen *et al.* [17], who studied iron absorption in women who were given meals with low calcium content (224 mg/day) or meals with milk, calcium lactate, or milk mineral isolate containing about 800 mg/day. All meals were labeled over a four-day period and iron absorption was measured by whole-body counting. No significant differences in iron absorption were found between the groups consuming the different levels and forms of calcium.

Does high calcium intake affect iron status in vulnerable populations?

It is generally accepted that many groups would benefit from increased intakes of calcium and many intervention studies have been conducted during the last decade. In several of these studies, iron status has also been determined. In some of these studies, calcium was given separate from meals and no effect on iron status was observed [18, 19], which is consistent with the lack of effect on iron absorption when calcium was given separate from meals [7]. However, there are also several studies in which calcium was given with meals and in which no significant effect on iron status was observed. Sokoll and Dawson-Hughes [20] gave premenopausal women 500 mg of calcium (as $CaCO_3$) twice daily for three months and found no change in hemoglobin or serum ferritin as compared to unsupplemented controls. Dalton *et al.* [21] increased the calcium intake of infants by 1200 mg/day by adding calcium glycerophosphate for 4–7 months and found no effect on hematocrits or serum ferritin as compared to controls. Kalkwarf *et al.* [22] gave lactating women 500 mg calcium (as $CaCO_3$) twice daily for 6 months and found no significant effects on hemoglobin or ferritin as compared to controls. Further, Minihane and Fairweather-Tait [23] gave adults 1200 mg of calcium (as $CaCO_3$) daily for 6 months and found no significant effect on hemoglobin, serum ferritin, or transferrin receptors as compared to controls. Finally, Mølgaard *et al.* [24] gave young adolescent girls (12–14 years) 500 mg of calcium (as $CaCO_3$) daily for one year and observed improved bone density in the calcium-supplemented groups, but no significant effect on hemoglobin or serum ferritin. Thus, to date, studies on calcium supplementation of various groups have failed to find any significant negative effect on iron status.

Why is iron absorption sometimes affected by high calcium intake, while there is no effect on iron status?

The answer to this question is not yet known, but it is highly likely that mechanisms regulating iron absorption will adapt to a high calcium intake and attempt to achieve iron homeostasis. It is well known that absorption of iron is tightly regulated and that iron status of an individual will affect iron absorption more than dietary factors [25]. Via a system of iron regulatory elements (IREs) on the mRNAs for ferritin and transferrin receptors, iron regulatory proteins (IRPs) will "sense" the cellular iron concentration and up- and down-regulate the expression of these proteins important for the cellular homeostasis of iron [26]. These two proteins are more involved in long-term regulation of homeostasis. Short-term regulation of iron absorption in the small intestine is achieved by two other proteins, divalent metal transporter 1 (DMT1) and ferroportin (FPN) [2]. Little is known about the response of these proteins to various factors other than iron status, but it is quite possible that they respond and adapt to changes in cellular calcium content. Although this needs to be demonstrated at the molecular level, a study in piglets strongly suggests that adaptation in iron absorption occurs as a response to changes in dietary calcium. Wauben and Atkinson [28] showed that when piglets were fed a high-calcium diet (4670 mg/L) or a normal-calcium diet (2000 mg/L), iron absorption as measured by a dual isotope technique was similar between the groups after 2 weeks. Similarly, no effect on iron status was observed. These investigators found that high calcium inhibited binding of ^{59}Fe to brush border membrane vesicles (BBMVs), and that this was similar in BBMVs from piglets fed high- or normal-calcium diets. This is consistent with the hypothesis that proteins involved in the intracellular metabolism of iron are affected by calcium, rather than the initial binding to the mucosal cell. An acute effect of calcium on iron absorption in rats has been shown by Barton *et al.* [29], who also suggested that calcium affects the intracellular metabolism of iron. This would also explain why some studies have shown that both non-heme and heme-iron absorption are acutely affected by calcium [5, 30]; as heme-iron is not released until heme has been internalized by the enterocytes, the calcium effect is likely to occur after initial uptake of iron by the cell [31].

We have investigated the potential adaptation of iron absorption to high calcium concentrations using the human intestinal Caco-2 cell line (Lonnerdal *et al.,* to be submitted). Briefly, Caco-2 cells were grown in Transwell chambers for 14 days until post-confluent. Formation of monolayers was confirmed by measuring transepithelial electrical resistance (TEER). Medium in the upper well (apical side) was replaced with serum-free medium (SFM) containing 1μM $FeSO_4$ (labeled with ^{59}Fe) together with 0 or 100 μM $CaCl_2$. After 1.5 and 4 hours, iron (^{59}Fe) in the top (apical) chamber and the bottom (basolateral) compartment was measured by gamma counting. Effects of Ca on DMT1 expression (apical Fe uptake), FPN expression and localization by antibody capture (serosal Fe efflux), and hephaestin expression and activity (Fe oxidation) were determined. DMT1 and FPN gene

expression was measured by quantitative reverse transcriptase-polymerase chain reaction (QRT-PCR) (or quantitative real-time….???) and protein expression by Western blotting as described earlier [32]. Hephaestin activity was analyzed by an in-gel colorimetric assay and using densitometry to quantitate any significant differences. We found a significant reduction in basolateral transfer of iron after both 1.5 and 4 hours, and slightly more iron in the apical chamber after 1.5 hours. Thus, there was an initial inhibitory effect of calcium on iron transfer across the epithelial cell, which most likely would cause an effect on iron absorption measured in single-meal studies, as iron largely has been absorbed within 4 hours after a meal. Expression of DMT1 was slightly reduced ($p = 0.06$) after 1.5 hours, but after 4 hours, it was significantly increased (Figure 1). There was no effect on total FPN after 1.5 hours, but surface-bound FPN was significantly decreased, suggesting re-localization of membrane-bound FPN into an intracellular compartment. It is well-known that the localization and therefore the function of FPN can be modulated by various conditions [33]. After 4 hours, FPN expression had increased slightly ($p = 0.06$) and more FPN was now located on the basolateral membrane (Figure 2). There was no significant effect of calcium on hephaestin expression or activity (data not shown). Although these studies need to be extended in time, it is apparent that there is an initial inhibitory effect of iron transfer across the intestinal cell and our results suggest that this is due to a transitory re-localization of FPN into an intracellular location, where it cannot transport iron. With time, FPN is transported back to the basolateral membrane, which should lead to a compensatory increase in iron transport from the cell to the systemic circulation. This may be accompanied by some down- and up-regulation of DMT1 and FPN. Thus, iron homeostasis may be achieved in dynamic changes in iron transporter localization and possibly expression.

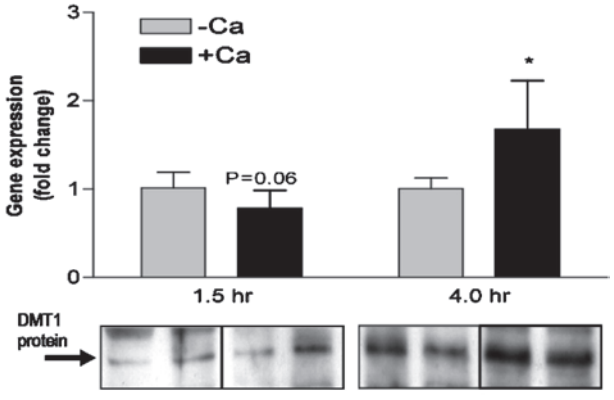

Figure 1: Expression of DMT1 mRNA (top panel) determined by QRT-PCR and protein (bottom panel) determined by Western blot (duplicate samples; left side, left panel – Ca, right panel at 1.5 h; right side, left panel – Ca, right panel at 4.0 h).

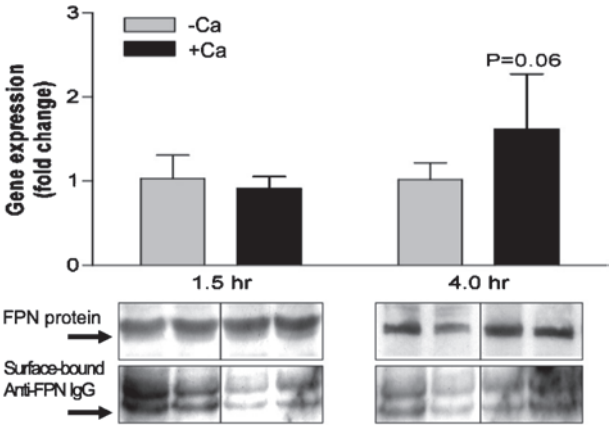

Figure 2: Expression of FPN mRNA (top panel) determined by Q-RT-PCR, total FPN protein (middle panel) determined by Western blot, and surface-bound FPN (bottom panel) analyzed by Western blot of the membrane fraction (duplicate samples; left side, left panel – Ca, right panel at 1.5 h; right side, left panel – Ca, right panel at 4.0 h).

Since calcium inhibits the absorption of both heme- and non-heme iron [5] and these two forms of iron are taken up at the apical membrane by two very different transporters, HCP1 and DMT1, respectively, we found it likely that the calcium effect would be exerted post-uptake; i.e. when iron released from heme by heme oxygenase intracellularly and ferrous iron transferred by DMT1 have formed a common iron pool. We therefore studied both FPN expression and its membrane localization. Recently, Thompson *et al.* [34] performed experiments similar to ours also using Caco-2 cells in monolayers. They found that the iron-induced increase in cellular ferritin was decreased by addition of calcium (2.5 mM). The localization of DMT1 changed, in that this transporter became intracellular when exposed to high calcium concentrations, but there was no change in total DMT1. Since these authors did not study FPN localization and we did not study DMT1 localization it is possible that both these events occurred in response to increased calcium exposure. An isolated effect on DMT1 localization, however, would not explain the effect of calcium on heme-iron absorption as DMT1 does not transport this form of iron. A potential effect of calcium on membrane structure/fluidity cannot be excluded, and needs to be studied further.

Conclusions

Calcium has been shown to affect iron absorption in some short-term studies, but not in all. In those studies, in which an effect has been observed, the magnitude of the effect varies considerably and appears to be dependent on the methodology chosen. While this interaction needs to be studied in detail at the molecular level, the total absence of any negative effect of iron status of vulnerable groups fed high levels of calcium with meals for long periods of time does not warrant any dramatic changes in our recommendations regarding calcium intake or how it is distributed among the meals during the day. Iron status of the population is, and should be, of concern. To take action after the "preponderance of data" has shown a negative effect on the parameter of concern (iron status) is scientifically prudent; to do so in anticipation of potentially negative consequences is not evidence-based and may cause public health problems instead of resolving them.

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