

Does calcium interfere with iron absorption?<sup>1,2</sup>

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Several animal studies have clearly shown that calcium interferes with dietary iron absorption and that addition of calcium to the diet may even induce iron deficiency (1, 2). Epidemiologic data also suggest that calcium interferes with iron absorption. In an extensive study in France ( $n = 1108$ ), serum ferritin and hemoglobin concentrations were negatively and significantly correlated with the intake of calcium (3). Similar findings were made in a study on French students ( $n = 476$ ) (4). In a longitudinal study in adolescent girls, high intake of calcium was associated with a lower serum ferritin concentration (5). However, inconsistent and conflicting results have been reported even when the methods and experimental design seem to be adequate. Moreover, the same research group has sometimes reported conflicting results. For example, one group found an inhibition of iron absorption by calcium in 2 studies (6, 7) but no effect in another (8). Similarly, we reported divergent results in 2 studies (2, 9). In this issue of *The American Journal of Clinical Nutrition* (10), 2 studies are presented on the effect of calcium on iron absorption with contradictory results. The question arises: Are there some special problems or pitfalls in studies on the interaction of calcium with iron absorption?

Most dietary factors influencing iron absorption probably exert their action within the gastrointestinal lumen by making iron more or less bioavailable for absorption. The effect of calcium, however, is different. The reported inhibition of iron absorption by calcium is the same for nonheme and heme iron (2, 11). Because heme and nonheme iron are absorbed by different receptors on the mucosal surface, inhibition by calcium must be located within the mucosal cell at some transfer step common to the 2 kinds of iron. This difference between calcium and other factors influencing iron absorption would by itself not cause methodologic problems.

The reported dose-effect relation between the amount of calcium given and the degree of inhibition of iron absorption (2) differs from other factors influencing iron absorption. No effect of calcium on iron absorption is seen when  $< 40$  mg Ca is present in a meal and no further inhibition is seen when the calcium content of the meal exceeds  $\approx 300$  mg. This flat, inverse S-shaped relation between the amount of calcium in a meal and the inhibition of iron absorption fits well with equations describing one-site competitive binding. In practice, this means that adding 200 mg Ca to a meal with, say, 100 mg Ca would reduce iron absorption by 40%, whereas no effect would be seen if the meal already contained  $\approx 300$  mg.

This dose-effect pitfall is illustrated by 2 studies. In an earlier study, we found that serving 250 mL milk with a hamburger

meal (already containing 220 mg Ca) did not significantly reduce iron absorption (9). The dose-effect relation was not known at that time. In another study no significant effect on iron absorption was observed when 150 mL milk or 125 g yogurt was added to a "typical French meal" already containing 320 mg Ca (12). These 2 studies contrast with other studies, including the present one (10), in which the effect of calcium on iron absorption was examined by direct measurements of iron absorption and in which an inhibiting effect of calcium on iron absorption was shown (2, 6, 7, 13–15).

There is one exception, however (8). In this study, iron absorption was measured from 2 main meals during 2, 5-d periods in 14 iron-replete subjects who modified their usual diet by decreasing or increasing their dietary calcium intake in the 2 periods. No statistically significant difference was seen when the mean absorption values were compared. The absence of an effect may be explained by comparing mean values instead of making pairwise comparisons in the same subjects.

The effect on iron absorption of giving calcium supplements was based in 2 studies on an expected decrease in iron stores measured by a decrease in serum ferritin concentration. In one randomized controlled study (16) in 57 healthy women, the effect on serum ferritin was examined when giving a calcium supplement (500 mg) with each of 2 daily meals. The initial mean serum ferritin concentration (34.9  $\mu\text{g/L}$ ) in the treatment group was lowered by 2.2  $\mu\text{g/L}$  after 12 wk, compared with an increase of 2.6  $\mu\text{g/L}$  in a control group. The changes were not significant. The same method was used in study 2 in the paper in the present issue (10). Calcium supplements of 400 mg were given with each of 3 daily meals for 6 mo in 11 iron-replete adults (7 women, 4 men). The daily calcium intake in the test group was reported to be 513–1522 mg (method not given). The initial serum ferritin concentration ( $46 \pm 7$   $\mu\text{g/L}$ ) did not change significantly during the study.

The validity of using changes in the concentration of serum ferritin as an indirect measure of changes in iron absorption has never been evaluated in iron-replete adult subjects. Several observations indicate that iron stores in iron-replete adult subjects are constant and difficult to change (17). This has also been

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shown when giving iron supplements to iron-replete subjects for a long time (18). Recent studies show a linear relation between the log of total amounts of iron absorbed and iron stores (calculated from serum ferritin) (17). Parallel regression lines were observed for diets with different bioavailability. Inserting data from observed regression equations into a simple conservation equation allows calculations of the rate of change of iron stores from known data about absorption and losses of iron. It is then evident that steady states for iron stores are formed in adults within 2–3 y and that these will take a long time to change (years) if absorption or losses are changed only moderately. Significant changes in serum ferritin after giving extra calcium with meals to adult, iron-replete subjects are therefore not expected within actual observation intervals and sample sizes.

By and large, studies on the effect of calcium on iron absorption based on direct measurements of iron absorption show that calcium inhibits iron absorption. The exceptions reported can be explained. Failure of the effect of calcium, when comparisons are based on changes in concentration of serum ferritin, can be explained by the fact that a long time and large amounts of materials are required to show the effect. The balance of evidence thus clearly indicates that calcium in amounts present in many meals inhibits the absorption of both heme and nonheme iron. A practical conclusion is that those with high iron requirements (eg, adolescents and menstruating and pregnant women) should try to restrict calcium intake with main meals, which contain most of the dietary iron, and that calcium supplements, when needed, should preferably be taken when going to bed. 

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