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The Effect of Calcium Consumption on Iron Absorption and Iron Status

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ABSTRACT

Recent increases in recommended calcium intakes recognize the important role of calcium in skeletal health, but many Americans, especially women, consume far less than recommended amounts. A potential drawback to encouraging increased calcium intake is suggested by the extensive literature showing an adverse effect of high calcium intake on dietary iron absorption, at least in short, highly controlled, experimental studies. However, the applicability of short-term studies involving test meals to long-term iron absorption and iron status is limited given the variety of foods and food combinations in self-selected diets and the ability of individuals to adapt to reduced iron intake. In general, studies of whole diets and studies conducted over several weeks tend to show no effect of increased calcium intake on iron absorption. In addition, experimental studies of calcium and iron status measures such as serum ferritin show no long-term effect of calcium supplementation on iron status. Prevention and treatment of iron deficiency should emphasize adequate consumption of iron-rich foods and, when indicated, the use of iron supplements. Recommended calcium intakes are important for skeletal health and do not appear to increase the risk for iron deficiency in healthy people. *Nutr Clin Care.* 2002;5:231–235

KEY WORDS: dietary calcium, calcium supplements, dietary iron, iron absorption, iron status

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Recent increases in recommended calcium intakes recognize the important role of calcium in skeletal health,[1] but many Americans, especially women, consume far less than recommended amounts.[2] A potential drawback to encouraging increased calcium intake is suggested by the extensive literature showing an adverse effect of high calcium intake on dietary iron absorption, at least in short, highly controlled, experimental studies. This article examines the evidence that increased calcium intake adversely affects long-term iron absorption and iron status in free-living individuals consuming self-selected diets.

Iron is essential for oxygen transport and storage, and is a critical component of numerous enzymes. Dietary iron is taken up by the intestinal mucosal cell and transferred across the cell to the blood where it is bound to transferrin. Absorbed iron can remain in the plasma bound to transferrin, be transported by transferrin to cells, or stored as ferritin. Absorption of iron, particularly nonheme iron, is affected by iron stores.[3-6] Hallberg et al. reported an inverse association between total iron absorption and serum ferritin up through serum ferritin concentrations of about 60 μg/L. At higher serum ferritin concentrations, iron absorption was reduced to the minimum needed to replace basal losses.[5]

Adult men lose about 1 mg of iron per day, mainly in the feces, and women lose about twice that during menstruation.[7] All groups incur iron losses with bleeding caused by injury and other medical conditions. Adequate dietary iron is needed to replace iron losses; chronically inadequate intake can lead to iron deficiency anemia. About 6% of Americans are in negative iron balance.[8] The groups most vulnerable to iron deficiency in the United States are toddlers (1-2 years) and women of child-bearing age (Table 1).[9] Iron deficiency and iron deficiency anemia also occur in older adults, often as a result of disease, but elevated iron stores appear to be the greater problem in this group.[10]

The fraction of consumed iron that is absorbed is affected by the bioavailability of the iron source (i.e., heme or nonheme) as well as the presence of other food components that enhance or inhibit iron absorption. Heme iron, obtained from animal sources, makes up only 10-15% of dietary iron in meat-eating populations, but, because of its higher bioavailability, provides nearly one-third of absorbed iron.[11] The heme complexes hemoglobin and myoglobin are absorbed unchanged and their iron is released in the mucosal cells of the intestine. Few dietary components are known enhancers or inhibitors of heme iron absorption. In contrast, nonheme iron, obtained from both animal and plant sources, must be soluble and in ionic form (ferrous or ferric) to be absorbed and its absorption is influenced by numerous dietary components. Meat, fish, poultry, and vitamin C all enhance nonheme absorption.[12,13] Other food components, including tannins in tea and coffee, phytates in cereals and legumes, and egg yolk, inhibit nonheme iron absorption.[6,13]

EFFECT OF CALCIUM ON IRON ABSORPTION

Numerous studies have demonstrated that supplemental and dietary calcium can inhibit iron absorption under a variety of test conditions. For example, calcium phosphate and calcium citrate in doses containing 600 mg of elemental calcium reduced absorption of an 18 mg ferrous sulphate dose by 62% and 49%, respectively, when both minerals were taken together without food.[14] Both these forms, as well as calcium carbonate, reduced iron absorption when taken with a meal, especially if the meal was low in iron and high in calcium.[14] Similarly, the amount of absorbed or retained iron was reduced when taken at one or more test meals with supplemental calcium carbonate,[15,16] calcium citrate malate,[17] or hydroxyapatite.[15]

Hallberg et al. conducted a series of experiments in which calcium chloride was added to bread rolls and consumed with a test meal.[18] This series demonstrated a dose-dependent association between calcium content and iron absorption from the test meal, with a maximal inhibition of about 60% for calcium doses up to about 300-600 mg. This study also showed a similar inhibition of heme and nonheme iron. This was interesting because there were no other known inhibitors or enhancers of heme iron absorption except meat, which enhances both heme and nonheme iron absorption.[19] Hallberg suggests that the inhibition of heme and nonheme iron occurs through the same mechanism—interference of iron transport through the mucosal cell.[20]

The applicability of short-term studies involving test meals to long-term iron absorption and iron status is limited by the variety of foods and food combinations in self-selected diets and by the apparent ability of individuals to adapt to reduced iron intake. Reddy and Cook[21] examined the effect of calcium intake on nonheme iron absorption from a complete diet. Fourteen healthy volunteers aged 19-37 consumed three different diets for five days each. One diet was self-selected; the others were designed to have increased and decreased calcium content, respectively. Calcium contents of the three diets averaged 280 mg, 684 mg, and 1281 mg per day, and the total iron contents were 10-11 mg per day for each diet. Iron absorption did not vary significantly across the calcium diets. Cook and colleagues examined the effects of three different types of diets on iron absorption in 45 volunteers aged 21-40.[22] One group consumed a self-selected diet over the two-week period. A second group consumed a diet designed to enhance iron absorption. This diet included added meat, fish, poultry, and vitamin-C-rich fruits and vegetables. A third group consumed a diet designed to inhibit iron absorption. This diet excluded red meat, limited other meats and vitamin-C-rich food, and included

Table 1. Prevalence of Iron Deficiency in the United States, NHANES III*

	Iron Deficiency, %†
Children age 1–2	9
Children age 3–11	2 to 3
Females 12–49	9 to 11
Females 50+	5 to 7
Males 12–49	<1 to 1

*From Looker, 1997.[9]
†Defined as having an abnormal value for at least two of three indicators: free erythrocyte protoporphyrin, transferrin saturation, and serum ferritin.

large amounts of legumes, cereals and foods rich in bran, and coffee or tea with every meal. The study showed the expected inhibitory and enhancing effects of single meals on iron absorption in fasting subjects. However, the inhibitory and enhancing effects of the whole diet were much smaller than those of the individual meals. The authors suggested that a number of characteristics of the whole diets might explain this difference, including variable iron content, shorter and more variable fasts preceding the meals, and effects of residual food in the gastrointestinal tract.

Consistent with this finding, Tidehag et al. found no effect of increased calcium intake from milk on iron absorption over one- to two-week periods in nine ileostomy patients who added milk to two of their four daily meals.[23] In contrast, Gleerup et al. found that 21 healthy females absorbed about 30% more iron from diet over 10 days when most of the calcium was consumed at two out of four meals compared to when the same amount of calcium was spread out evenly across the four meals.[24]

The potential importance of evaluating the effect of calcium consumption on iron absorption over even longer periods is suggested by a recent study of Hunt and Roughead.[25] This study examined the fractional absorption of nonheme and heme iron over 10 weeks of consumption of high and low bioavailable iron diets. At baseline, about 0.49 mg per day of nonheme iron was absorbed from the high bioavailability diet compared with 0.10 mg per day from the low bioavailability diet. After 10 weeks, absorption from the two diets had become more similar, with 0.30 mg per day absorbed from the high bioavailability diet and 0.15 mg per day from the low bioavailability diet; the adaptation was more pronounced in subjects with lower serum ferritin concentrations. Calcium contents of the two diets were similar. No comparably long intervention studies have examined the inhibitory effect of dietary calcium on iron absorption.

EFFECT OF CALCIUM ON IRON STATUS

From a clinical standpoint, any effects of calcium intake on iron absorption are important only insofar as they increase the risk for iron deficiency. A few large observational studies and many small experimental studies have examined associations of calcium intake with various indicators of iron status. A large French observational study reported inverse correlations of dietary calcium intake in a population that included males and females ranging in age from 6 months to 97 years. The magnitude of these associations cannot be computed with certainty from the information given, but they appear to be small. In addition, age and sex subset analyses were not conducted to determine whether the associations were similar across groups.[26] Total calcium intake from diet and supplements was not associated with serum ferritin in elderly Framingham Heart Study participants.[27]

Experimental studies in various age groups do not provide evidence that calcium supplementation has a negative impact on iron status. Healthy infants given iron-fortified formula with 1800 mg versus 465 mg of calcium showed no differences over four months in four measures of iron status.[28] Similarly, in preschool children, no difference in red blood cell incorporation of iron was observed after five weeks on a high calcium diet (about 1000 mg per day) versus a low calcium diet (about 500 mg per day).[29] Effects of calcium supplementation on iron status of premenopausal women were recently reviewed by Bendich, who concluded that calcium supplementation as high as 1200 mg per day does not affect iron status in healthy premenopausal women.[30] Ilich-Ernst et al. 1998 saw no effect in adolescent girls of supplementation with 1000 mg ca per day (as calcium citrate malate) taken after breakfast and before bedtime for four years on serum ferritin or red blood cell indexes.[31] Plasma ferritin of premenopausal women given 1000 mg per day of calcium as carbonate for 12 weeks did not differ from that of untreated controls.[32] Lactating women have higher postpartum iron stores than nonlactating women because of delayed return of menses, but supplementation with 500 mg of calcium (as carbonate) twice a day with meals from 6–12 months postpartum had no effect on serum ferritin of women regardless of lactation status[33] Similar results were found in 60 lactating Gambian women who took 100 mg per day of calcium carbonate between meals.[34] A small study in iron replete men and women found no effect of supplementation with 1200 mg per day of calcium (as carbonate) for six months on functional iron measures (hemoglobin and hematocrit) or iron stores (plasma ferritin).[16] Nine men given 780 mg of calcium (as gluconate) with phosphate for 39 days had no change in plasma iron, plasma transferrin, or serum ferritin.[35]

CLINICAL IMPLICATIONS

Although calcium interferes with iron absorption when the two minerals are taken together, high calcium intake does not appear to adversely affect iron absorption or iron status over the long term in healthy people who eat a varied diet. Some investigators recommend that persons at risk for iron deficiency should consume iron-rich foods and calcium-rich foods (or supplements) at different times of day,[36,37] and it is possible that this approach might benefit some individuals. Routine screening for low iron stores is an important preventive measure, especially in high-risk populations such as women of child-bearing age. Prevention and treatment of iron deficiency should emphasize adequate consumption of iron-rich foods and, when indicated, the use of iron supplements.

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Iron: Tolerable Upper Intake Levels

HAZARD IDENTIFICATION

Iron is a redox-active transition metal. In health, it is carried from one tissue to another bound to transferrin and stored in cells in the form of ferritin or hemosiderin. These proteins hold iron in the ferric state. Kinetic restrictions prevent the iron from being reduced by cellular reductants, and it is thus shielded from unwanted participation in redox reactions (McCord, 1996). If the transport and storage mechanisms are overwhelmed, the free iron will immediately be chelated by cellular compounds, such as citrate or adenosyl diphosphate, that readily participate in redox reactions catalyzing the formation of highly toxic free radicals or the initiation of lipid peroxidation.

Adverse Effects

Acute Effects

There are reports of acute toxicity resulting from overdoses of medicinal iron, especially in young children (Anderson, 1994; Banner and Tong, 1986; NRC, 1979). Accidental iron overdose is the most common cause of poisoning deaths in children under 6 years of age in the United States (FDA, 1997). Vomiting and diarrhea characterize the initial stages of iron intoxication. With increasing time after ingestion, at least five organ systems can become involved: cardiovascular, central nervous system, kidney, liver, and hematologic (Anderson, 1994). The severity of iron toxicity is related to the amount of elemental iron absorbed. Symptoms occur with doses between 20 and 60 mg/kg with the low end of the range associated primarily with gastrointestinal irritation while systemic toxicity occurs at the high end (McGuigan, 1996). These data, however, are not used because acute intake data are not considered in setting a UL.

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Iron-Zinc Interactions

High intakes of iron supplements have been associated with reduced zinc absorption as measured by changes in serum zinc concentrations after dosing (Fung et al., 1997; Meadows et al., 1983; O'Brien et al., 2000; Solomons, 1986; Solomons and Jacob, 1981; Solomons et al., 1983). However, plasma zinc concentrations are not considered to be good indicators of body zinc stores (Whittaker, 1998). Studies using zinc radioisotopes showed reduced zinc absorption when both minerals were administered in the fasting state at an iron-zinc ratio of 25:1 but not at 1:1 or 2.5:1 (Sandstrom et al., 1985). When iron and zinc supplements were given with a meal, however, this effect was not observed. Other investigators have reported similar observations (Davidsson et al., 1995; Fairweather-Tait et al., 1995b; Valberg et al., 1984; Walsh et al., 1994; Yip et al., 1985). A radioisotope-labeling study by Davidsson and coworkers (1995) showed that fortifying foods such as bread, infant formula, and weaning foods with iron had no effect on zinc absorption. In general, the data indicate that large doses of supplemental iron inhibit zinc absorption if both are taken without food, but do not inhibit zinc absorption if they are consumed with food. Because there is no evidence of any clinically significant adverse effect associated with iron-zinc interactions, this effect is not used to determine a UL for iron.