

# Calcium Supplementation and Iron Status of Females

Adrienne Bendich, PhD

*From SmithKline Beecham Consumer Healthcare, Parsippany, New Jersey, USA*

Iron balance is regulated in part by the level of iron absorption, which is influenced by iron stores and the level of erythropoietic activity. In short-term absorption studies, dietary calcium and supplemental doses of calcium chloride or calcium carbonate inhibited iron absorption from concomitantly consumed meals. In contrast, several long-term intervention studies of the effect of calcium supplementation on iron status in populations at potentially high risk for compromised iron status failed to show reductions in various indicators of iron status including serum ferritin levels. The evidence suggests that long-term consumption of calcium supplements does not affect overall iron status. An adaptive response, possibly involving an upregulation in the efficiency of iron absorption, has been suggested as a possible explanation for the disparity between the results from short- and long-term studies. *Nutrition* 2001;17:46–51. ©Elsevier Science Inc. 2001

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## INTRODUCTION

Iron is essential for several crucial physiologic functions including transporting and storing oxygen, carrying electrons, and catalyzing various reactions ranging from oxidative metabolism to cellular proliferation. The metabolism of iron is highly conserved in healthy people as the body has limited capacity to excrete excess iron. Iron balance is regulated by the control of absorption, which is influenced by the amount of iron in body stores and the level of erythropoietic activity.<sup>1</sup> Loss of iron occurs with certain conditions such as menses, pregnancy and consequent iron transfer to the fetus, and bleeding due to injury, infection, or other causes. Women with child-bearing potential represent a risk group for lower-than-recommended iron status and anemia (due to frank iron deficiency).

Calcium is the major structural component in bone and teeth. Calcium is also required for many important physiologic functions such as cell proliferation, responses to hormones, and release of neurotransmitters.<sup>2</sup> The metabolism of calcium is tightly regulated by parathyroid hormone, calcitonin, and vitamin D to maintain serum calcium concentration and prevent deleterious neurologic, gastrointestinal, and renal effects.<sup>2,3</sup> Low-calcium intake causes a release of calcium from bone and increases the risk of osteoporosis. The most critical time for increasing bone-mineral density for women is before age 30 y, although consumption of recommended levels of calcium during adulthood is also necessary for bone health.

Several short-term studies have recently shown that concurrent ingestion of calcium and iron from the same meal inhibits iron absorption. Some of these studies have used food sources of calcium and others have used supplemental calcium; both sources reduced iron intakes from single meals. Long-term studies of calcium supplementation, however, do not indicate that iron status in women was decreased.

A major randomized, double-blind, placebo-controlled clinical trial demonstrated that 1200 mg of supplemental calcium carbonate (CaCO<sub>3</sub>) per day significantly reduced the symptoms of premenstrual syndrome in women of child-bearing age.<sup>4</sup> Because this particular female population is often also at risk for low iron status as a consequence of menstruation and low iron intake, it is important to examine the effects of calcium supplementation on the iron status of menstruating women.

Thus, this article reviews the data from studies that have examined the short- and long-term consequences of calcium intakes (at or above recommended levels, mainly from supplements) in women who may be at risk for low iron status.

## REGULATION OF IRON METABOLISM

The main function of iron metabolism is to recycle iron released from destroyed erythrocytes and incorporate this iron into the hemoglobin in newly formed erythrocytes (erythropoiesis). Iron is tightly conserved as it moves from circulating red blood cells (e.g., hemoglobin) to iron stores (e.g., ferritin); there are also separate tissue iron pools (e.g., myoglobin and enzymes), labile iron pools, and iron-transport proteins, such as transferrin. The predominant iron carrier in blood is transferrin, which is found in the plasma and extracellular fluid. Transferrin carries iron to the bone marrow, where iron is incorporated into newly formed erythrocytes; transferrin also transfers iron from the monocyte-and-macrophage system, where iron is released from the erythrocyte. Iron binds again to transferrin and is carried to the bone marrow. With each cycle, a small amount of iron is added to the stores in the form of ferritin; a small proportion of the storage iron is also passively released into the plasma. Conservation of iron is not 100% efficient, and there is a daily loss of iron in urine, sweat, and feces and through blood loss. In the presence of a negative iron balance, iron is absorbed from the small intestine to replace the iron that has been lost.<sup>1</sup>

## ABSORPTION, UPTAKE, AND TRANSPORT

In healthy individuals who have minimal iron loss, normal iron balance is regulated by the control of iron absorption occurring in the small intestine. Iron is taken up by mucosal cells lining the

Correspondence to: Adrienne Bendich, PhD, Associate Director of New Product Research, SmithKline Beecham Consumer Healthcare, 1500 Littleton Road, Parsippany, NJ 07054-3884, USA. E-mail: adrienne.4.bendich@sb.com

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TABLE I.

INDICES OF IRON STATUS	
Indices	Significance
Red blood cell count	Measures number of red blood cells in the blood
Hemoglobin	Measures the concentration of the iron-containing protein in red blood cells
Hematocrit	Measures the volume of red blood cells in 100 mL of blood
Mean corpuscular volume	Determines the volume of red blood cells
Erythrocyte zinc protoporphyrin	Indicates the iron availability to bone marrow over the period in which circulating red blood cells are produced
Plasma transferrin	Measures the quantity of iron-transport protein in plasma and other non-binding proteins
Total iron-binding capacity	Measures the concentration of transferrin in plasma
Serum iron	Measures the quantity of iron bound to transferrin
Transferrin saturation	Measures the proportion of binding sites on transferrin occupied by serum iron
Serum ferritin	Correlates with iron stores

intestinal lumen, exits these cells, and enters the capillaries, where it is bound to transferrin. Transferrin transports iron in the blood and delivers iron to cells via the transferrin receptor. Newly absorbed iron can remain bound to transferrin in the plasma, it can remain within cells as intracellular iron, or it can be stored as ferritin. When intake is low and iron is not available for absorption, ferritin iron is released to maintain the level of iron required for erythropoiesis. To prevent excess iron accumulation, ferritin binds iron that is absorbed by the epithelial cells of the small intestine. The bound iron is then excreted in the feces when the small-intestinal lining is sloughed off.<sup>1</sup>

## THE BASIS OF AN INDIVIDUAL'S IRON STATUS

There is no single sensitive and specific indicator of overall iron status. Thus, investigators use a variety of indirect methods to estimate iron status (Table I). Indices such as red-blood-cell count, hemoglobin concentration, hematocrit (Hct), mean corpuscular volume (MCV) of the red blood cell, and erythrocyte zinc protoporphyrin (ZPP) are used to evaluate erythropoiesis and heme synthesis, which are processes that are highly dependent on iron status. Serum iron concentration, total iron-binding capacity of transferrin, and transferrin saturation are indices that evaluate the concentration of iron in the blood. Serum ferritin is another index that is considered very useful because it is a reflection of iron stores. Because these tests have different specificities and sensitivities in detecting iron deficiency, several methods are generally employed to establish overall iron status.<sup>1</sup>

## STUDIES EXAMINING THE EFFECTS OF CALCIUM SUPPLEMENTATION ON ACUTE IRON ABSORPTION

Single- and multimeal absorption studies are common methods to identify the potential for mineral-to-mineral interactions. Hallberg et al.<sup>5</sup> initiated a study to 1) examine the effect of calcium on heme-iron absorption from a meal containing meat versus heme-

iron absorption from a meatless meal and 2) compare the effect of calcium on non-heme and heme absorption from a meal containing meat. During the first phase of the iron-absorption study, hamburger containing hemoglobin (source of heme iron) labeled with radioactive iron (<sup>55</sup>Fe or <sup>59</sup>Fe) and bread rolls (source of non-heme iron) were given with or without CaCl<sub>2</sub> (165 mg of calcium) to 28 volunteers (12 men, 16 women) aged 24 to 65 y for 4 consecutive days. In the second phase of the study, bread rolls containing hemoglobin labeled with radioactive iron (<sup>55</sup>Fe or <sup>59</sup>Fe) were given with and without CaCl<sub>2</sub> (165 mg of calcium) to the same volunteers over the same duration. In the third phase of the study, two servings of hamburger containing hemoglobin labeled with radioactive iron (<sup>55</sup>Fe) and non-heme-labeled (<sup>59</sup>Fe) FeCl<sub>3</sub> were given with or without CaCl<sub>2</sub> to 10 volunteers before determining iron absorption.

CaCl<sub>2</sub> significantly reduced heme-iron absorption from the hamburger meal and the meatless meal containing heme iron (41% and 48%, respectively). In addition, CaCl<sub>2</sub> inhibited heme-iron absorption to the same extent as that seen with non-heme-iron absorption in a previous study.<sup>6</sup> A previous report found a dose-dependent inhibitory effect of calcium on iron absorption. Doses below 40 mg of calcium had no effect; maximal inhibition of 50% to 60% occurred with up to 300 mg of calcium, with no further inhibition at higher amounts, suggesting an incomplete block of iron absorption.<sup>6-8</sup> These important results demonstrate that 1) calcium has a direct rather than an indirect effect on heme-iron absorption and counteracts the enhancing effect of meat on heme-iron absorption and 2) calcium appears to interfere with mucosal intracellular transport of iron along a part of the pathway that is common for heme-iron and non-heme-iron transport.<sup>5</sup> A previous study suggested the possibility that the interference of calcium with iron absorption is not luminal but rather affects the intracellular metabolism of iron.<sup>9</sup> These findings were further supported by an iron-bioavailability study in anemic rats, where high dietary CaCO<sub>3</sub> significantly lowered mucosal Fe transfer.<sup>10</sup>

In a second study, the effect of CaCO<sub>3</sub> supplementation (400 mg of calcium per meal) on the absorption of iron consumed concurrently was examined in healthy volunteers (*n* = 14, 11 women and 3 men) ages 20 to 69 y.<sup>11</sup> Using stable iron isotopically labeled and fecal monitoring, CaCO<sub>3</sub> supplementation was shown to significantly reduce non-heme-iron absorption compared with consuming the meal without calcium supplementation (15.8% ± 2.1% versus 4.7% ± 1.4%, *P* < 0.001).

## STUDIES EXAMINING CALCIUM AND IRON DOSING SCHEDULES

Because the results of short-term mineral-to-mineral interaction studies have suggested a potential for similar long-term effects of calcium on iron absorption, several studies examined the potential for an optimal dosing schedule for calcium and iron. In a single-meal study, Gleerup et al.<sup>12</sup> investigated the duration of the inhibitory effect of calcium on iron absorption by giving volunteers natural sources of dietary calcium at various times before giving an iron-containing meal. Twenty-one volunteers ages 19 to 65 y (7 men, 14 women) were initially given either water or calcium from milk and cheese (340 mg of elemental calcium) as part of a breakfast meal. Either 2 or 4 h later, the volunteers were given a meal consisting of hamburger and a roll containing FeCl<sub>3</sub> labeled with <sup>55</sup>Fe or <sup>59</sup>Fe (2.1 mg of iron, 30 mg of calcium, <5 mg of phytate phosphate). Mean iron-absorption ratio of a meal with milk and cheese versus a meal without milk and cheese given 2 h before the iron-containing meals was 0.99, which was not significantly different from 1 (*t* = 0.14, *P* > 0.05).<sup>12</sup> Using the single-meal absorption test, this study demonstrated that consuming dietary calcium at least 2 h before a meal did not affect the absorption of iron from an iron-containing meal.

These investigators also examined the effects of divided daily calcium intakes on iron absorption from complete meals containing iron consumed over two 10-d periods by 21 healthy female volunteers aged 21 to 44 y.<sup>7</sup> Daily calcium intake (937 mg), which was predominantly from milk and cheese, was either distributed between breakfast and a late evening meal or evenly divided across breakfast, lunch, dinner, and an evening meal. Total mean iron intake from all meals consumed during the 10-d period was 13.3 mg (11.9 mg of non-heme iron). The total amount of iron absorbed when the calcium was distributed only between breakfast and the evening meal was 34% greater than when the calcium was distributed across all of the four meals ( $P = 0.0072$ , one-sample sign test).<sup>7</sup> The investigators concluded that separation of calcium from dietary intake of iron would improve iron absorption. Of importance, there was no evidence of a negative effect of calcium supplementation for 10 d on iron status.

## RELEVANCE OF SINGLE-MEAL STUDIES

The body of evidence suggests an acute inhibitory effect of calcium on iron absorption. However, the results of controlled single-meal studies may exaggerate the effect on iron absorption and may not predict the long-term effects of calcium on iron status. Some studies have shown that conventional meals reduce this calcium effect less than the meals provided in single-meal studies.<sup>11,13</sup> Cook et al.<sup>14</sup> examined the effect of a self-selected diet versus diets designed to maximally enhance or inhibit non-heme-iron absorption. Known dietary enhancers (e.g., ascorbic acid) or inhibitors (e.g., phytate) were used in the designed meals. The enhancing and inhibiting effects of calcium on iron in single-meal studies was shown to be exaggerated compared with findings from self-selected diets. This disparity may be due to a dilution of the effects of enhancers and inhibitors of iron absorption when these are part of a normal diet.<sup>13,14</sup>

The effect of high and low calcium intake on the non-heme-iron absorption from a varied diet was studied during a 5-d radioiron-labeling period; no difference in iron status was shown.<sup>11,15</sup>

Given that several dietary factors affect the absorption of iron, it is necessary to determine whether single-food analysis could be used as a guideline for predicting iron bioavailability from complex meals containing several food items. After the analysis of several dietary factors, a regression equation based on co-consumption of meat, phytic acid, and ascorbic acid (vitamin C) was proposed as an effective estimate of potential non-heme-iron absorption from typical Western meals.<sup>16</sup> Tidehag et al.<sup>17</sup> tested the validity of the single-meal method over 8 wk. Ileostomy subjects were selected to reduce the possibility of random errors when conventional balance techniques are used. The addition of a high-calcium (milk) diet had no effect on apparent iron absorption.<sup>17</sup>

## FORM OF CALCIUM

In addition to meal composition, the type of calcium salt used may be a factor in the extent of the interference in iron absorption. Two studies used whole-body retention of <sup>59</sup>Fe to measure the effect of various calcium sources in postmenopausal women.<sup>18,19</sup> In one study, 500 mg of elemental calcium as calcium carbonate or hydroxyapatite significantly reduced iron absorption when administered with test meals.<sup>18</sup> The effects of several other sources of calcium were examined by Deehr et al.<sup>19</sup> Calcium as a mixed calcium citrate-malate salt in the form of a pill (CCM), CCM in orange juice (high ascorbic acid-containing food), and milk were selected. Compared with placebo, iron absorption was significantly reduced with milk and CCM; CCM plus orange juice did not reduce iron absorption. The inhibiting effect of calcium from milk

was greater than that with CCM. These results reflect the presence of known enhancers (e.g., ascorbate and citrate) of iron absorption, counterbalancing the inhibiting effect of calcium.

## CALCIUM SUPPLEMENTATION AND STUDIES OF LONG-TERM EFFECTS ON IRON STATUS

Several studies have explored whether long-term calcium supplementation compromises iron status. Snedeker et al.<sup>20</sup> examined iron utilization for 39 d in nine adult males fed diets supplemented with different levels of calcium as calcium gluconate and phosphorus as glycerol phosphate. Dietary-supplementation levels included 1) 780 mg of calcium plus 843 mg of phosphate, 2) 780 mg of calcium plus 2442 mg of phosphate, and 3) 2382 mg of calcium plus 2442 mg of phosphate. Although subjects in group 3, who were fed the high level of calcium and phosphate, excreted significantly more iron in their urine than did subjects fed the other two diets ( $P = 0.05$ ), fecal iron excretion and apparent absorption of iron did not differ significantly among the three treatment groups. In addition, the three diets did not significantly affect plasma iron, plasma transferrin, or serum ferritin ( $P > 0.05$ ). The investigators concluded that the addition of high levels of calcium and phosphate for 39 d did not significantly alter iron status in these men.<sup>20</sup> We have no reason to assume that these results would be different if the subjects were menstruating women.

Several investigators have explored the long-term effects of calcium supplementation in female populations (Table II). Sokoll and Dawson-Hughes,<sup>21</sup> in a study of 57 premenopausal women, administered 1000 mg of elemental calcium per day as CaCO<sub>3</sub> for 12 wk; the control group ( $n = 52$ ) did not take a placebo. The percentage of change in plasma ferritin in the calcium-treated group ( $-2.2 \pm 38.4$ ) was not significantly different than the percentage of change in the control group ( $2.6 \pm 39.7$ ;  $P > 0.05$ ). At week 12, serum iron, serum total-iron-binding capacity, transferrin saturation, hemoglobin, and Hct were not significantly different between the two groups. Furthermore, comparisons of the various iron-status indices for the control and calcium-treated groups at baseline and at week 12 were not different. The investigators concluded that a 12-wk period of calcium supplementation (1000 mg/d) did not significantly compromise iron status in healthy premenopausal women.<sup>21</sup>

Minihane and Fairweather-Tait<sup>11</sup> investigated the effects of calcium supplementation on iron status in iron-replete healthy volunteers consuming a Western-style diet. Subjects were given 1200 mg of elemental calcium daily (400 mg of calcium taken with each meal;  $n = 11$ ) or were unsupplemented ( $n = 13$ ) for 6 mo. Hct, hemoglobin, and erythrocyte ZPP in the calcium-treated group were not significantly different than in the control group ( $P > 0.05$ ). At 0 and 6 mo, the mean values for Hct, hemoglobin, and ZPP for the calcium-treated group were virtually unchanged: 0.412 and 0.416, 139 and 136 g/L, and 222 and 226  $\mu$ g/L, respectively. The functional iron indices were not significantly altered in the control group during the 6-mo period, with the exception of ZPP, which decreased significantly ( $P > 0.05$ ). The investigators concluded that long-term, moderate-to-high calcium supplementation did not affect iron status in iron-replete adults consuming a Western-style diet.<sup>11</sup>

Minihane and Fairweather-Tait proposed an adaptive mechanism in the intestinal mucosal cell to explain the apparent inconsistency between the short-term effects of calcium on iron absorption and the lack of long-term effect on iron status. They hypothesized that mature mucosal cells in the presence of a continuous low supply of iron are stimulated to produce high-affinity proteins that result in more efficient iron absorption by the enterocytes.<sup>11</sup> Hallberg et al.<sup>22</sup> hypothesized that there has not been sufficient time for the evolution of intestinal mechanisms regulating iron absorption to adapt to the present low-energy and low iron

TABLE II.

Study	Study population	Mean age (y)	Treatment groups	n subjects	Dose of calcium* (mg/d)	Duration of study (m)	Mean serum ferritin concentrations†		P	
							Initial (µg/L)	Final (µg/L)		
Sokoll and Dawson-Hughes <sup>21</sup>	Premenopausal females	33	Calcium	57	1000	3	35 ± 28	-2.2 ± 38	>0.05	
		31	None	52			47 ± 42	2.6 ± 40		
Minihane and Fairweather-Tait <sup>11</sup>	Healthy iron-replete volunteers	43	Calcium	11‡	1200	6	47 ± 7	50 ± 7	>0.05	
		44	None	13§			40 ± 7	38 ± 7		
Yan et al. <sup>25</sup>	Lactating females	28	Calcium	30	1000	12	20.5 ± 2.6¶	14.8 ± 2.3#	>0.05	
		28	Placebo	30			15.9 ± 2.3¶	12.5 ± 2.2#		
Kalkwarf and Harrast <sup>26</sup>	Lactating females**	30	Calcium	38	1000	6	47.7††	30.5	>0.5‡‡	
								28.4#		
			31	Placebo	38			47.7††	30.5	
								27.5#		
	Non-lactating females**	31	Calcium	40	1000	6	31.5	25.5	>0.5‡‡	
			31	Placebo	42			31.5	25.5	
								27.5#		
Ilich-Ernst et al. <sup>27</sup>	Premenarchial females	11§§	Calcium	177	1000	48	29.1 ± 1.3	29.6 ± 1.9	0.96	
			Placebo	177			29.3 ± 1.4	29.5 ± 1.6		

\* Calcium supplements taken with meals unless otherwise indicated.

† Values are reported as arithmetic mean ± standard deviation unless otherwise indicated; indicates the percentage of change.

‡ Seven females and four males.

§ Ten females and three males.

|| Calcium supplement taken between meals, 5 d/wk.

¶ Nine days postpartum.

# Values are reported as geometric means.

\*\* Six months postpartum.

††  $P < 0.001$  versus non-lactating females.

‡‡ Comparison of geometric means across lactation groups.

§§ Mean age of study population ( $n = 354$ ).

||| Calcium supplements taken after breakfast and before bedtime.

intakes generally seen in populations at risk for iron deficiency. Others, however, have argued that iron stores are highly regulated and difficult to change in iron-replete subjects. Therefore, using the changes in the concentration of serum ferritin as an indirect measure of changes in iron status in these individuals is inappropriate unless the study is of considerable duration (years) and involves a larger sample size.<sup>8</sup> However, a recent study in a laboratory animal model using labeled iron has provided further data in support of the existence of an adaptive response to high calcium intake. Wauben and Atkinson reported that high calcium intake did not affect either the percentage of iron absorbed or iron status in infant piglets fed a diet high in calcium (liquid piglet formula fortified with calcium glycerophosphate; 4666 mg of calcium per liter) for 2 wk. The investigators hypothesized that there is an upregulation of iron transfer across the intestinal brush border in the presence of high calcium intake.<sup>23</sup> It is important to note that this animal model is considered by the investigators as a reflection of the effects of calcium in a model of marginal iron status. Thus, even when iron status is low, calcium supplementation did not further reduce iron status.<sup>24</sup>

Two studies have investigated the effect of calcium supplementation on iron status in lactating women. In a randomized, double-blind, placebo-controlled intervention study, Yan et al.<sup>25</sup> examined the effect of long-term consumption of calcium supplements on iron status in lactating Gambian women, habituated to low-calcium diets. Women who were 9 d postpartum received either CaCO<sub>3</sub>

(1000 mg of elemental calcium per day;  $n = 30$ ) or placebo ( $n = 30$ ) that was to be taken between meals (5 d/wk) for 1 y. No significant difference in plasma ferritin concentrations was observed.<sup>25</sup> Consistent with the data from the acute-absorption study by Gleerup et al.,<sup>7</sup> this study showed that the potential for calcium to inhibit iron absorption was minimized when the calcium was taken between meals.

In the second study in lactating women, Kalkwarf et al.<sup>26</sup> examined the long-term effects of consuming CaCO<sub>3</sub> with meals on iron status in lactating women from Cincinnati, Ohio, who were 6 mo postpartum. Women who breast-fed five times daily and provided no more than one supplemental formula feeding per day were entered into the study. The women weaned their infants from breast milk approximately 2 mo after enrollment. Non-lactating women were defined as those who either gave their infants only formula from birth or breast-fed for no more than 2 wk postpartum. Lactating ( $n = 38$ ) and non-lactating ( $n = 40$ ) groups received either 1000 mg of calcium in the form of CaCO<sub>3</sub> or placebo ( $n = 38$  lactating and  $n = 42$  non-lactating). The supplements were taken with meals for 6 mo. The geometric mean serum ferritin concentrations across lactation groups in either the calcium or placebo groups at 12 mo were not significantly different (28.4 µg/mL and 27.5 µg/mL, respectively;  $P > 0.5$ ). In addition, there were no significant changes in mean hemoglobin concentration, mean corpuscular volume, and Hct across the four groups ( $P \geq 0.3$ ). At baseline, lactating women had significantly higher serum

ferritin concentrations than did non-lactating women (47.7  $\mu\text{g/L}$  versus 31.5  $\mu\text{g/L}$ , respectively). After weaning and, presumably, the concomitant resumption of menstruation, serum ferritin concentrations decreased by 17  $\mu\text{g/L}$  in lactating women. At 12 mo postpartum, geometric mean serum ferritin concentrations were not significantly different across all lactating ( $n = 76$ ) and non-lactating ( $n = 84$ ) women (30.5  $\mu\text{g/L}$  versus 25.5  $\mu\text{g/L}$ , respectively;  $P = 0.14$ ). This study provided important data concerning the effect of lactation on indices of iron status and further confirmed the lack of interference of calcium supplementation on iron status.<sup>25,26</sup>

Another study examined the effects of calcium supplementation on iron status of female children (average age = 11 y). In a double-blind, placebo-controlled intervention study, Ilich et al.<sup>27</sup> examined the effects of calcium supplementation on growth, menstrual status, and iron status in premenarchial females during 4 y of intervention. Subjects received either CCM (1000 mg of elemental calcium per day) or placebo tablets that were taken after breakfast and in the evening before bedtime. Mean serum ferritin concentrations for the calcium-supplemented group at baseline and years 1, 2, 3, and 4 ranged from 29.1  $\mu\text{g/L}$  to 31.1  $\mu\text{g/L}$ . The mean serum ferritin concentrations of the placebo group at baseline and years 1, 2, 3, and 4 ranged from 29.3  $\mu\text{g/L}$  to 33.8  $\mu\text{g/L}$ . There were no significant differences in serum ferritin concentrations at any point between the two groups (all  $P > 0.05$ ). In addition, hemoglobin, Hct, red-blood-cell count, mean corpuscular volume, and mean corpuscular hemoglobin concentration were not significantly different between the groups over the 4 y ( $P > 0.05$ ). During adolescence, there is a higher demand for iron for growth due to the expansion of iron-rich cellular compartments. Changes in lean body mass correlated with the rate of growth and were shown to be a predictor of serum ferritin concentration ( $P < 0.0001$ ); increased gains in lean body mass correlated with decreased serum ferritin levels. Duration of menstrual bleeding correlated with decreases in mean corpuscular volume and hemoglobin ( $r = -0.273$ ,  $P < 0.007$  and  $r = -0.164$ ,  $P < 0.04$ , respectively). The investigators concluded that iron stores are negatively affected by the pubertal growth spurt and menstrual status but not by long-term calcium supplementation in adolescent females with relatively low iron intakes (<9 mg/d).<sup>27</sup> A similar effect was also seen in a recent epidemiologic study of girls and young women that examined the influence of dietary calcium on iron status. A cross-sectional design using 3-d food records in six European countries found a weak, non-significant inverse association between dietary calcium intake and iron status. There was also no dose-response trend detected.<sup>28</sup>

Lonnerdal<sup>13</sup> cited a study involving Danish adolescent girls, 12 to 13 y of age, presented as an abstract at the 1998 International Dairy Congress, Aarhus, Denmark. No effect on hemoglobin or serum ferritin was seen after daily supplementation with 500 mg of calcium carbonate for 1 y.<sup>13</sup>

A recent study showed no adverse effect in the incorporation of iron into red blood cells in small children following a high-calcium diet.<sup>29</sup> Eleven preschool children, 3 to 5 y old, participated in a multitracer, cross-over study. After a 5-wk adaptation period to either a low or high calcium diet, <sup>44</sup>Ca and <sup>58</sup>Fe were given orally with meals, and <sup>46</sup>Ca was given intravenously. Blood samples were taken 14 d postdosing for isotope ratio measurements. Increasing calcium intake from 500 mg/d to 1200 mg/d resulted in significant absorption of calcium without the impairment of iron status.<sup>29</sup>

Further research is needed to determine whether calcium intake at recommended levels for women with child-bearing potential (1000 to 1300 mg/d)<sup>30</sup> affects iron repletion in women who are anemic or have low iron status. Because studies in laboratory animals have suggested that iron status is not compromised in a model of marginal iron status, it is expected that there will be similar effects in individuals.<sup>24</sup> However, such studies are still

needed to ensure that calcium supplementation does not compromise iron repletion in those with low iron stores.

## CONCLUSIONS

The totality of the evidence from the studies reviewed indicates that supplementation with calcium, at the levels found to reduce symptoms of premenstrual syndrome<sup>4</sup> and enhance bone-mineral density<sup>2</sup> (1200 mg/d), does not affect normal iron status in healthy menstruating females. There are also studies suggesting that, in healthy premenarchial girls, toddlers, and infants with normal iron status, calcium supplementation does not reduce iron status.<sup>27,29,31</sup>

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**The Indian Society for Parenteral and Enteral Nutrition (ISPEN) VIIth Annual Conference**, Ahmedabad, India. To register, contact: Dr. S.S. Alurkar, Secretary, ISPEN-Gujarat Chapter, 301, 3rd Floor, Arth Complex, B/h. Rama Motors, Mithakhali Six Roads, Ahmedabad - 380 009, India. Tel: 079-6426777. E-mail: alurkar@indiatimes.com. Website: www.hostindia.com/ispen

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