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The inhibitory effect of soy products on nonheme iron absorption in man[1-3]

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ABSTRACT Radioiron absorption studies were performed in male volunteer subjects to determine the effect on nonheme iron absorption of various semipurified proteins. When egg albumen and casein were substituted in protein-equivalent quantities in a semisynthetic meal, similar mean absorptions of 2.5 and 2.7% were observed. In contrast, isolated soy protein reduced absorption sharply, to an average of 0.5%. When egg albumen in the semisynthetic meal was replaced with full fat soy flour, textured soy flour, and isolated soy protein, absorption fell from 5.5 to 1.0, 1.9, and 0.4%, respectively, indicating an inhibitory effect by a wide range of soy products. The effect of substituting textured soy flour for meat in a meal containing a hamburger, french fries, and a milkshake was also evaluated. With 3:1 and 2:1 ratios of meat to unhydrated textured soy flour, absorption decreased by 61 and 53%, respectively. The soy products tested in this study have a pronounced inhibitory effect on the absorption of nonheme iron. *Am. J. Clin. Nutr.* 34: 2622–2629, 1981.

KEY WORDS Iron absorption, isolated soy protein, textured soy flour, full fat soy flour

Introduction

The majority of clinical studies has shown that protein facilitates the absorption of dietary nonheme iron. Animal tissue including fish and poultry are especially important not only because they contain assimilable heme iron (1–3) but also because they enhance absorption of nonheme iron from foods eaten in the same meal (4–7). However, not all sources of protein enhance iron absorption. For example, egg yolk has been shown to impair iron absorption (8, 9) and dairy products in general have a relatively inhibitory effect on nonheme iron absorption (5).

We recently reported the results of iron absorption studies in which the effect of doubling or deleting the sources of carbohydrate, fat, and protein in a semisynthetic meal were examined (10). Egg albumen, the protein source, had an inhibiting effect on iron absorption whereas the content of fat or carbohydrate had little influence. To determine whether this inhibition was unique to egg albumen, we examined in this study the effect of other semipurified proteins including casein and isolated soy protein. Several soy products were found to inhibit markedly the absorption of nonheme iron in human subjects.

Methods

Subjects

Three separate studies were performed in 36 men ranging in age from 18 to 50 yr. Study I (15 subjects) compared the effect of different semipurified proteins; study II (10 subjects) examined the influence of various soy products on iron absorption; study III (11 subjects) evaluated the effect on iron absorption of adding soy protein to meat. All of the volunteers were in good health and denied a history of gastrointestinal disorders that might affect iron absorption. Iron status was normal,

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with the exception of one subject who had a serum ferritin of 12 ng/ml indicating depleted iron stores (11). Written consent was obtained from each volunteer and all procedures were carried out in accordance with the standards of the Human Subjects Committee of the University of Kansas Medical Center.

Absorption measurements

Three or four separate iron absorption tests were performed in each subject using double sequential radioiron labels. Test meals were administered between 7 and 9 AM after an overnight fast, and only water was allowed for the subsequent 3 h. All meals were labeled extrinsically by adding varying quantities of $FeCl_3$ in 1.0 ml 0.01 N HCl containing either 2 μCi ^{59}Fe or 5 μCi ^{55}Fe (12, 13). On the 1st day of each study, blood was drawn for measurements of serum ferritin (14) and background blood radioactivity. The first pair of test meals were tagged separately with either ^{59}Fe or ^{55}Fe and administered on 2 consecutive days. Blood was obtained 14 days later to measure incorporated red cell radioactivity and a second pair of separately tagged meals were again given on successive days. Subjects in study I were given only one additional test meal after the initial pair of measurements. A final blood sample was drawn 2 wk after the last test meal to measure the increase in circulating red cell radioactivity. All radioiron measurements were performed on duplicate 10-ml samples of whole blood using a modification of the method of Eakins and Brown (15). Percentage absorption was calculated on the basis of blood volume estimated from height and weight (16) and an assumed red cell incorporation for absorbed radioactivity of 80% (17).

Test meals

All meals in studies I and II were comprised of semipurified ingredients (**Table 1**). They represent modifications of the semisynthetic meal used in previous studies (5, 18) except that no inorganic calcium or phosphate was added. In study I, each meal contained 68 g carbohydrate derived from dextrimaltose, 35 g fat from corn oil, and 29.4 g protein from various sources. The protein in meal A was supplied as egg albumen (Monark Egg Corp., Kansas City, MO), in meal B as sodium caseinate (National Casein Sales, Chicago, IL), and in meal C as isolated soy protein (ISP) (Supro 710, Ralston Purina Co., St. Louis, MO). ISP is the spray-dried washed precipitate that is recovered after the water extract of defatted soybean flour has been adjusted to pH 4.5, the isoelectric point of the soy protein.

In study II, the carbohydrate and fat components of the meals were the same as for study I, but each meal contained only 14.7 g protein. This was supplied in meals A through D as albumen, full fat soy flour (El Molino Mills, City of Industry, CA) (FSF), textured soy flour (Supro 50A, Ralston Purina Co.) (TSF), and ISP respectively. TSF is obtained by the extrusion of defatted soy flour. Sufficient $FeCl_3$ was added to each meal in studies I and II to provide a final iron content of 4.1 and 4.0 mg, respectively.

The components of each of the meals in studies I and II were thoroughly mixed and served as a drink with the exception of the TSF meal (meal C, study II). In the latter, the dry TSF granules were hydrated in a styrofoam bowl with twice their weight of water and warmed for 45 s in a microwave oven. The fat and carbohydrate components were mixed and a portion poured over the TSF granules which were then eaten with a spoon. The remaining carbohydrate and oil mixture which contained the radioiron was taken as a drink.

The effect of partial substitution of meat with TSF was examined in study III. Meals A, B, and C each contained 55 g french fried potatoes, 180 ml vanilla milkshake, a meat patty containing varying amounts of TSF, and a bun. Meal A contained 100 g lean ground beef (precooked weight). In meal B, 30 g dry TSF granules were added to 100 g beef while meal C contained the same quantity of TSF but only 70 g beef. This resulted in weight ratios of meat to unhydrated TSF of approximately 3:1 in meal B and 2:1 in meal C and protein ratios of 1.2 and 0.8, respectively. In meals B and C, TSF was moistened with an equal quantity of water and then mixed with the raw ground beef. All patties were broiled for 5 to 7 min per side, refrigerated overnight, and heated in a microwave oven immediately before serving. The hamburger meals were tagged extrinsically by adding 0.1 mg iron as labeled $FeCl_3$ to the milkshake. The final test (meal D) in study III consisted of a reference dose of 3 mg iron as $FeSO_4$ and sufficient

TABLE 1
Protein and iron content of semipurified meals

	Meal	Protein substitute				Iron	
		Source	Weight	Protein content	Protein substitute	$FeCl_3$	Total
			g	g	mg	mg	mg
Study I							
	A	Albumen	36.7	29.4	0.4	3.7	4.1
	B	Casein	32.6	29.4	0.3	3.8	4.1
	C	Soy (ISP)	33.9	29.4	4.0	0.1	4.1
Study II							
	A	Albumen	18.4	14.7	0.1	3.9	4.0
	B	FSF	40.4	14.7	3.4	0.6	4.0
	C	TSF	28.6	14.7	3.3	0.7	4.0
	D	ISP	17.0	14.7	2.0	2.0	4.0

γ

freshly prepared ascorbic acid solution to give a 2:1 molar ratio of ascorbate to iron (6, 19). The purpose of this measurement, which has been used extensively in prior iron absorption studies in human subjects, is to standardize measurements of nonheme iron absorption in subjects with varying iron status.

Statistical analysis

Because of the highly skewed distribution of iron absorption measurements when expressed as a percentage of the administered dose, absorption data were converted to logarithms for statistical analysis and the results were reconverted to antilogarithms to recover the original units (20). When comparing any two test meals in the same study, a paired *t* test was used to determine whether mean log absorption values differ significantly from 0 which is equivalent to testing whether the mean ratio in percentage absorption differ from 1.

Results

The effect of three semipurified protein sources on iron absorption (study I) is shown in **Table 2**. Geometric mean absorption in meal A containing egg albumen averaged 2.49%. This is somewhat higher than previously observed values for this meal, which presumably reflects the omission of inorganic calcium and phosphate (21). Mean absorption from meal B containing sodium caseinate was nearly identical to that with egg albumen, averaging 2.74% (mean ratio B/A = 1.10). In contrast, absorption from meal C containing ISP was much lower, averaging only 0.46% (mean ratio C/A = 0.19, $p < 0.001$).

A comparison of the effect of different soy products on iron absorption (study II) is summarized in **Table 3**. Mean iron absorption from meal A containing egg albumen averaged 5.5%. This value is higher than that from the similar meal in study I, reflecting the lower albumen content in this study (10). In all three meals containing soy products in study II, iron availability was markedly reduced and in all instances the differences with meal A were highly significant. With FSF (meal B) absorption averaged 0.97% (mean ratio B/A = 0.18). Inhibition of iron absorption from TSF (meal C) was somewhat less pronounced, averaging 1.91% (mean ratio C/A = 0.35). The lowest iron absorption occurred in meal D containing ISP with a mean absorption of 0.41% (mean ratio D/A = 0.08). Thus, when soy products were substituted for albumen in equivalent protein quantities, percentage nonheme iron absorption was reduced by 82, 65, and 92% with FSF, TSF, and ISP, respectively. In study II, the difference in absorption between the three meals containing soy products were also statistically significant. Absorption with TSF was significantly higher than with either FSF (mean ratio C/B = 1.95, $p < 0.01$) or ISP

TABLE 2
Effect of protein concentrates on iron absorption (study I)

Subject	Age	Packed cell volume	Serum ferritin	Iron absorption			Absorption ratio	
				ALB* (A)	Casein (B)	Soy (C)	B/A	C/A
		%	ng/ml	% of dose				
1	29	47	61	0.97	1.00	0.16	1.03	0.17
2	26	50	34	1.26	1.11	0.07	0.88	0.06
3	27	46	59	1.40	1.40	1.70	1.00	1.22
4	25	45	164	1.41	1.21	0.56	0.86	0.40
5	26	43	31	1.43	4.12	0.36	2.94	0.25
6	25	46	46	1.55	1.83	0.18	1.19	0.12
7	25	44	94	1.63	6.43	0.30	4.00	0.18
8	25	43	51	1.80	1.06	0.27	0.59	0.15
9	25	49	88	2.26	2.41	0.95	1.08	0.42
10	28	50	48	3.78	1.26	0.52	0.33	0.14
11	30	43	55	4.51	6.03	0.56	1.35	0.12
12	24	44	37	4.82	8.37	1.16	1.75	0.24
13	25	46	45	6.25	4.43	0.12	0.71	0.02
14	26	48	114	6.50	2.78	1.03	0.43	0.16
15	26	44	12	7.51	20.45	4.97	2.78	0.66
Mean†	26	46	53	2.49	2.74	0.46	1.10	0.19‡
			−1 SE	2.08	2.16	0.35	0.92	0.15
			+1 SE	2.98	3.47	0.62	1.31	0.24

* ALB, egg albumen.
† All values are geometric means except age and packed cell volume.
‡ $p < 0.001$.

3

(mean ratio C/D = 4.62, $p < 0.001$). Absorption with FSF was also significantly higher than with ISP (mean ratio B/D = 2.37, $p < 0.01$).

The effect of partial substitution of TSF for meat was examined in study III (**Table 4**). With meat alone (meal A), absorption averaged 3.2% with a range of 0.48 to 14.61%. When 30 g TSF was added to the same quantity of meat (meal B), absorption fell to 1.24%, a highly significant decrease (mean ratio B/A = 0.39, $p < 0.001$). When the meat content was reduced in proportion to the quantity of added soy (meal C), absorption was slightly higher, averaging 1.51%. The difference in absorption from this meal and meal A containing no soy was also highly significant (mean ratio C/A = 0.47, $p < 0.001$). Thus, in meals containing a meat to soy ratio of 3:1 and 2:1, the decrease in absorption due to TSF averaged 61 and 53%, respectively. In these iron-replete men, reference absorption (meal D) averaged 19.88%. Absorption of nonheme iron from meals A,

TABLE 3
Effect of various soy products on iron absorption (study II)

Subject	Age	Packed cell volume	Serum ferritin	Iron absorption				Absorption ratio		
				ALB* (A)	FSF (B)	TSF (C)	ISP (D)	B/A	C/A	D/A
		%	ng/ml	% of dose						
1	24	44	83	2.01	0.81	1.00	0.16	0.40	0.49	0.07
2	21	46	105	3.28	0.91	0.90	0.52	0.27	0.27	0.15
3	35	40	149	3.46	0.40	1.71	0.28	0.11	0.49	0.08
4	24	46	59	3.75	1.52	3.30	0.61	0.40	0.88	0.16
5	42	42	94	4.11	0.46	1.47	0.13	0.11	0.35	0.03
6	25	47	30	5.53	0.57	2.40	0.17	0.10	0.43	0.03
7	24	44	112	6.08	1.21	2.82	0.33	0.19	0.46	0.05
8	24	46	46	8.37	4.67	2.73	1.27	0.55	0.32	0.15
9	34	46	86	14.03	0.66	1.06	1.55	0.04	0.07	0.11
10	25	42	26	18.36	1.85	4.43	0.72	0.10	0.24	0.03
Mean†	28	44	69	5.50	0.97	1.91	0.41	0.18‡	0.35‡	0.08‡
			−1 SE	4.42	0.77	1.60	0.31	0.14	0.28	0.06
			+1 SE	6.83	1.23	2.27	0.54	0.23	0.43	0.09

* ALB, egg albumen.
† All values are geometric means except age and packed cell volume.
‡ $p < 0.001$.

TABLE 4
Effect of soy protein on iron absorption from a meal containing beef (study III)

Subject	Age	Packed cell volume	Serum ferritin	Iron absorption				Absorption ratio		
				100 g beef (A)	Beef soy 3:1 (B)	Beef soy 2:1 (C)	REF* (D)	B/A	C/A	B/C
		%	ng/ml	% of dose						
1	36	44	60	0.48	0.13	0.25	17.80	0.27	0.52	0.52
2	22	44	70	1.43	1.16	0.18	14.05	0.81	0.75	1.07
3	18	39	33	2.30	1.16	1.22	17.91	0.50	0.53	0.95
4	19	44	59	2.41	0.78	0.60	7.73	0.32	0.24	1.30
5	18	48	41	3.10	1.06	0.85	31.95	0.34	0.27	1.24
6	18	46	61	3.47	1.55	3.25	23.43	0.44	0.93	0.47
7	19	49	60	3.76	1.31	1.75	13.71	0.34	0.46	0.74
8	37	41	51	3.81	0.88	0.91	7.88	0.23	0.23	0.96
9	18	48	61	3.91	0.82	0.91	19.46	0.20	0.23	0.90
10	20	46	31	10.76	6.47	8.08	36.85	0.60	0.75	0.80
11	29	49	27	14.61	7.87	15.62	95.83	0.53	1.06	0.50
Mean†	23	45	48	3.20	1.24	1.51	19.88	0.39‡	0.47‡	0.82‡
			−1 SE	2.43	0.89	1.06	16.02	0.34	0.40	0.73
			+1 SE	4.21	1.72	2.17	24.68	0.44	0.56	0.91

* REF, reference dose.
† All values are geometric means except age and packed cell volume.
‡ $p < 0.001$.

4

B, and C therefore averaged 16, 6, and 8% of the reference dose absorption, respectively.

Discussion

The inclusion of soy products caused a significant inhibition of iron absorption from all meals in this study (**Fig. 1**). The immediate question posed by these results is the contrast with earlier investigations that indicated a relatively high bioavailability for soybean iron. For example, animal studies using the hemoglobin-repletion method in rats have shown a relative biological value of 60 to 80% for soy products (22). However, it is known that iron absorption measured in small laboratory animals does not always reflect bioavailability for human beings. For example, Fitch et al. (23) observed that rhesus monkeys developed iron deficiency anemia when placed on diets containing ISP but not when fed casein-based diets with comparable levels of protein and iron. These workers also demonstrated that radioiron absorption from ISP was less than half that from casein.

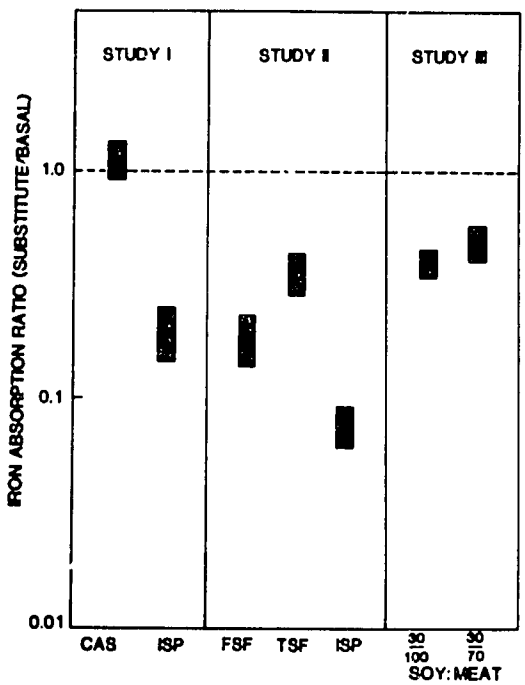

FIG. 1. The effect of semipurified proteins on nonheme iron absorption. Absorption ratios of soy product: albumen are plotted for studies I and II. For study III, absorption ratios are plotted for meals containing varying weight ratios of soy to meat. The height of each *bar* represents ±1 SE.

A number of human studies have also shown relatively high iron availability from meals containing soybean that had been hydroponically labeled with radioiron. For example, Moore (24) reported a mean absorption of 18% in seven normal subjects and values of 20 to 25% in patients with iron deficiency anemia. In a study comparing iron absorption from a variety of food items, a mean absorption of 11% was observed in 17 subjects given intrinsically labeled soy (19). Sayers et al. (25) later reported a mean absorption of 20% from intrinsically labeled soybean meals given to five iron-deficient subjects.

However, not all human studies have shown this relatively high absorption of intrinsically labeled soybean. Ashworth et al. (26), in a study of 10 infants, observed a geometric mean absorption of 2.6% for boiled soybean; when the soybean was baked before administration to 16 infants, mean absorption was 6.7%. Bjorn-Rasmussen et al. (27) recorded an absorption of 2.62% when soybeans were given to 15 normal subjects, three of whom were women. Geometric mean absorption in this study was 1.53%, a value well within the range of absorption observed in the present study.

The cause of this wide difference in iron absorption from hydroponically labeled soybean is unknown. In four separate studies with different batches of the same variety of tagged soybean, absorption ranged from 2.7 to 11.0% (28) (**Table 5**). This broad range is not explained by differences in iron status because the absorption ratio of soybean to reference varied from 0.11 to 0.46.

Other workers have not demonstrated diminished absorption from soy-based diets. In a study by Rios et al. (29), in 4- to 7-month-old infants, mean absorption of fortification

TABLE 5
Absorption of hydroponically-tagged soybean

No. of subjects	Iron absorption*		Absorption ratio
	Soybean	Reference	
17	11.0	25.8	0.46
15	2.7	25.5	0.11
7	9.8	44.3	0.22
11	5.7	38.0	0.15
Mean	6.1	29.4	0.21

* All values are geometric means.

5

iron added to a soy-based formula was 5.4% as compared to 3.4% from a milk-based formula. The relatively high proportion of fortification iron (ferrous sulfate) in this study may have masked an inhibiting effect. Young and Janghorbani (30) recently measured iron absorption from a soy-based diet using a fecal balance technique and ^{58}Fe as an extrinsic tag. An exceptionally high absorption of 21 ± 6% was observed which the investigators attributed to a generous but unspecified ascorbic acid intake with each meal. Van Stratum and Rudrum (31) found no effect on serum iron levels, iron binding capacity, or transferrin saturation in 92 healthy volunteers fed a diet containing 25% protein derived from soy protein foods. Since these iron parameters do not become abnormal until iron stores are exhausted (32), and since iron deficiency develops slowly in the absence of blood loss, one would not expect these measurements to show a difference.

This variability in iron absorption from soybean meals is perplexing. One difference between previous studies and ours is that our meals were extrinsically tagged whereas most earlier studies used intrinsically tagged soybean. However, this observation does not explain the low absorption in this study because in each instance where a discrepancy has been noted between extrinsic and intrinsic tagging, the extrinsic label was better absorbed. In 11 subjects given intrinsically tagged soybean, absorption averaged 6.3% from the intrinsic label as compared to 7.8% from an extrinsic label in the same meal (12). The 27% higher absorption in that study may be explained by the fact that the extrinsic tag was taken as a drink and not mixed with the food; other workers have observed extrinsic to intrinsic tag ratios of 1.04 with soybean meals (27). It therefore seems unlikely that the lower absorption values for soy products observed in the present study relate to the extrinsic tag method.

Other differences between earlier studies and this report lie in the nature of the meals and the methods used for preparing them. The semisynthetic meal contained both fat and carbohydrate whereas soybean was administered alone in many prior studies. Moreover, in some of the latter the soybeans were baked; it is noteworthy that in the studies by Ashworth et al. (26), baking resulted in a more than 2-fold increase in percentage iron absorption from soybean. We have also found a significant increase in iron absorption from baked soy products (T. A. Morck, S. R. Lynch, and J. D. Cook, unpublished observations). Processing soybean to obtain higher protein-containing products cannot be excluded as a factor in the inhibition of iron absorption. Although TSF rather than FSF gave the highest iron absorption in study II, (1.91%), the product with the highest protein content (ISP) gave the lowest iron absorption (0.41%). Since all three meals in study II were prepared on an equal protein basis, the results suggest that the processing of whole beans to obtain the three products altered their influence on food iron absorption.

While our results demonstrate that soy products may, under some circumstances, depress iron absorption significantly, the mechanism of the inhibition is unknown. Phytate is believed to have a strong inhibiting effect on iron absorption (33). We did not measure phytate levels of the soy fractions but they are known to contain relatively high amounts of phytate; ISP has been reported to contain 1.86% phytic acid (22). However, in a recent study with whole wheat bran, we found that the inhibiting effect of bran was not lessened when it had been dephytinized (34). Moreover, while fully iron saturated phytate is insoluble at neutral pH, it has been shown that more than half of the iron in wheat bran is present in the form of monoferric phytate, an iron complex soluble at neutral pH (35). Monoferric phytate is absorbed by dogs equally as well as food iron (36). Further studies will be necessary before phytate can be implicated in the inhibition of nonheme iron absorption caused by soy products.

The implications of our findings in relation to iron status in the population are uncertain because of the complexity of dietary factors that influence nonheme iron absorption. In this country, soy is increasingly used as a meat extender and in meals containing meat, nonheme iron is readily available (3). In addition, the heme portion of meat is absorbed independently, and is not impaired by factors that reduce nonheme iron absorption (2). Therefore, one would expect the inhibiting effect of soy in people consuming a relatively large proportion of animal tissue to be quite limited.

6

Inhibition of iron absorption by soybean derivatives is more likely to be an important problem in areas where soy constitutes the major source of protein, especially if the diet contains little meat or ascorbic acid. We have recently reported that infant protein supplements such as corn-soya-milk, which contain a high proportion of soy protein, may not supply sufficient iron for normal nutritional needs of children (37). There is little doubt that soy is a valuable and relatively inexpensive source of dietary protein. The inhibitory effect on iron absorption reported here does not detract from this important property but does emphasize the need to evaluate the adequacy of iron in diets containing significant amounts of soy products. It seems likely that the deleterious effects with respect to iron nutrition could be circumvented by the addition of fortification iron to these diets or perhaps the addition of an enhancer of iron absorption such as ascorbic acid.

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