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Soy and Osteoporosis

Consumption of Soyfoods May Reduce Risk of Osteoporosis

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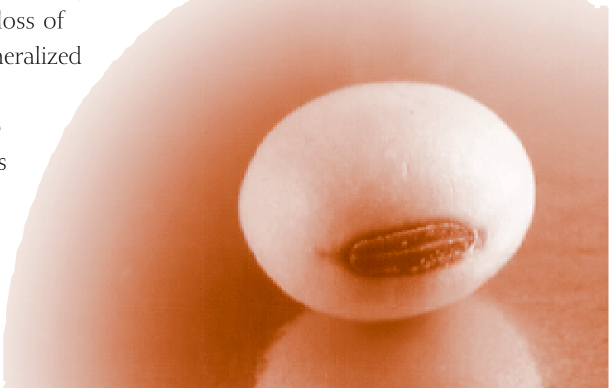
Postmenopausal women over 50 years of age are especially vulnerable to osteoporosis due to the rapid and progressive bone loss associated with estrogen deficiency at menopause, followed by sustained bone loss with aging. Some women experience an early menopausal acceleration of bone loss of 1-3% per year (1-3), followed by an age-related bone loss of approximately 0.7-1% per year (4-6). Osteoporosis can be defined as a systemic disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a subsequent increase in bone fragility and susceptibility to fracture. Estrogen Replacement Therapy (ERT) has been used effectively in stabilizing skeletal bone mineral density and preventing vertebral fractures (7-8). However, due to undesirable side effects and potential health risks, the compliance to ERT by postmenopausal women is only 10-20% (9) and the search for alternatives is ongoing.

Phytoestrogens and Osteoporosis

While research to date is not conclusive, results indicate that phytoestrogens may provide an alternative to ERT as a favorable therapeutic agent in the treatment of osteoporosis. Phytoestrogens, including isoflavones, are estrogen-like molecules abundant in plants (10). One of the richest sources of isoflavones is the soybean and soyfoods. Isoflavones, the most studied phytoestrogens related to bone health, possess weak estrogenic activity and have an affinity for estrogen receptors, specifically estrogen receptor-ß (ER-ß) which is present in bone, brain, bladder and vascular epithelia.

The limited amount of data on the skeletal effects of isoflavones suggests agonistic effects. Ecological studies show a lower incidence of hip osteoporosis among Asian populations consuming high soy diets in comparison to Western populations (11). Studies using the ovariectomized rat model have shown comparable bone-sparing effects of 17ß-estradiol and soy protein isolate (12), genistein or daidzein (13), or their respective succinylated products obtained after soybean fermentation (14). Arjmandi et al. (15) showed that feeding isolated soy protein increased mRNA IGF-I biosynthesis, suggesting that IGF-I levels would increase. IGF-1 is a protein involved in the bone formation process; therefore, an increase in IGF-1 is indicative of increased bone formation. Anderson et al. (16) demonstrated a biphasic response of genistein on ameliorating bone loss in lactating, ovariectomized rats, suggesting estrogen agonistic action only at low doses and possible antagonistic action at high doses. When purified isoflavones were given daily to rats at 10 ug/g body weight, daidzein was more efficient than genistein in preventing ovariectomy-induced bone loss of cancellous bone which is porous, spongy bone tissue, although genistein was equally effective in reducing loss of cortical bone which is compact, highly mineralized bone tissue (17).

There have been two short-term (six to nine month) published studies of the effects of soy isoflavones on bone density in humans. Both studies used soy protein isolate with isoflavones as the treatment.



Potter et al. (18) studied 66 hypercholesterolemic postmenopausal women and Alekel et al. (19) studied 69 perimenopausal women. Both studies reported a positive effect with approximately 90 mg isoflavones/day on spine bone mineral density (BMD) of one to two percent relative to control women fed a milk-protein. In the work of Alekel et al. (19), no significant loss in spine BMD occurred in women fed isolated soy protein enriched in isoflavones or soy protein isolate in which isoflavones had been removed by alcohol extraction, whereas a loss did occur in the women who received whey protein. In contrast to these two studies, Gallagher et al. (20) showed no advantage of the soy isoflavone containing protein at the same dose in postmenopausal women.

Biomarkers of bone turnover are useful to determine changes in bone formation and bone resorption. An increase in markers of bone formation indicates that bone is being deposited, while an increase in markers of bone resorption indicates that bone is being degraded. Bone biomarkers are a useful tool in the assessment of metabolic bone disease and therapeutic efficacy. Wangen et al. (21) found that markers of bone turnover were affected by soy isoflavones at 65 and 130 mg/day in both pre- and postmenopausal women. In premenopausal women, markers of bone resorption significantly increased on both isoflavone diets and in postmenopausal women bone formation markers were significantly decreased on both isoflavone diets. The changes observed in this study were of small magnitude and not likely to be clinically significant. A current clinical study in humans is assessing the effects of soy isoflavones on calcium metabolism, including kinetics. This information is essential in ascertaining the mode of action for the skeletal effects of isoflavones.

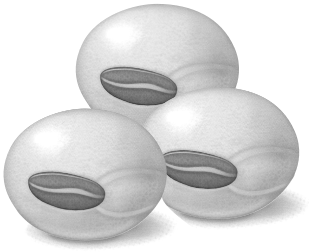
Soy Protein and Urinary Calcium

The profile of sulfur-containing amino acids determines the effect of protein on urinary calcium excretion (22). Relative to animal protein, soybeans have a lower content of the sulfur-containing amino acids cystine and methionine. However, relative to other legumes, soybeans have a higher content of sulfur-containing amino acids (23). The following table shows the amounts of sulfur-containing amino acids in various protein sources.

Table 1. Amounts of sulfur-containing amino acids in various protein sources[a]

Source	Amount (mg/g)
Legumes[1]:	
Soybean	30
Black, Great Northern, Kidney, Navy, Pink, Pinto, Small white, and White	26
Chick pea	27
Cow pea	25
Lentil	22
Lima, Baby and Large	24
Fruit	38
Cereals	28
Animal foods	39
Nuts and seeds	46

[a] Adapted from Young (24).



Metabolism of sulfur-containing amino acids generates sulfate which increases urine acidity and therefore urinary calcium excretion. Whiting and Draper (25) showed that the generation and urinary excretion of sulfate in rats is a major factor in protein-induced hypercalciuria, i.e., urinary calcium excretion above the normal 100-200 mg calcium/day range in U.S. adults. In addition, they found that the variability in urinary calcium excretion was related to differences in sulfur amino acid content of the protein diets. Schuette et al. (26) showed high degrees of correlation between urinary sulfate and total renal acid excretion and urinary sulfate and urinary calcium excretion in elderly men and postmenopausal women using purified proteins, i.e., proteins isolated from whole foods.

Similarly, Zemel et al. (27) found that an addition of purified sulfur amino acids to a protein diet significantly increased urinary calcium excretion in adult males. Breslau et al. (28) further demonstrated significant urinary calcium, urinary sulfate and net acid excretions in an animal protein-rich diet relative to ovo-vegetarian and vegetarian diets.

The ovo-vegetarian and vegetarian diets contained soymilk, soy cheese and textured vegetable protein. There were no significant differences in urinary chemistry between the two vegetarian diets.

Regardless of the presence of sulfur-containing amino acids, vegetarian diets tend to have an alkaline ash residue that predictably would result in lower urinary calcium excretion than acid generating diets. In contrast to the Breslau et al. study, Kunkel et al. (29) found no significant differences in urinary sulfate excretion between vegetarians and nonvegetarians although there were significant differences in the intake of animal and plant protein as well as in total protein intake. Preliminary results of a randomized, metabolically controlled crossover study in postmenopausal women indicated that a soy protein diet significantly reduced urinary calcium excretion relative to a milk protein control diet. Because the only difference between the diets was the source of protein, the reduction in urinary calcium excretion in the soy protein diet was due to lower sulfur-containing amino acids (30).

In a Michigan study of Caucasian Seventh Day Adventists, Marsh et al (31) showed that younger paired Caucasian lacto-ovo-vegetarian (LOV) and omnivore women had no statistically significant differences in bone mineral density. However between 50-87 years of age, omnivores had 35% less bone mass and vegetarians had 18% less bone mass than the younger paired women. The calcium: phosphorus ratio was 0.81 for the LOV group and 0.66 for the omnivore group ($p<0.001$). The significance of the ratio is that dietary phosphorus content rises as dietary protein intake increases. Furthermore, calculations of the acid or base excesses of the customary self-selected diets indicated that the LOV diet was a basic diet whereas the omnivore diet was an acidic diet.

In additional studies of Caucasian Seventh Day Adventists from various parts of the United States and Canada attending an annual meeting, Marsh et al. (31) further distinguished the various types of vegetarian diets. Results indicated that the lowest bone mineral density by age 80-89 years was in the total vegetarian dietary group (0.433 g/cm^2, N=2). The LOV group that consumed meat at least once/week followed with a bone mineral density of 0.470 g/cm^2 (N=2) and a mean milk intake of 470 mL. Bone densities and number of subjects for lifetime LOV, LOV ≥ 20 years and, LOV with fish and chicken were 0.553 g/cm^2, (N=10); 0.502 g/cm^2, (N=13); and 0.569g/cm^2, (N=3), respectively. Corresponding mean milk intakes were 450 mL, 430 mL, and 430 mL.

Although there were insufficient numbers of subjects to establish statistical significance, the study is significant in that it emphasized the differential effects of various types of vegetarian diets on bone mineral density. The study suggested that a LOV lifestyle might have a protective factor in preventing osteoporosis. Additionally, the study suggested a geographical effect on bone mineral density, i.e., 16 Caucasian vegetarian (all types) women from the Michigan study attended the annual meeting and showed the highest bone mineral density of 0.585 g/cm^2. The authors suggested a heightened awareness of bone mineralization through on-going studies in the vicinity and the presence of hard-water in the Berrien Springs area.

A more recent study showed that elderly women with a high dietary ratio of animal to vegetable protein intake have a more rapid femoral neck bone loss and a greater risk of hip fracture than those with a low dietary ratio of animal to vegetable protein (32). However, Heaney (33) pointed out that a body of literature has proven that protein tends to have a positive effect on bone overall. Specifically, Heaney mentioned a study conducted by Hannan et al. (34) using the Framingham data that indicated a greater bone loss over a 4-year period in individuals with the lowest protein intakes, similar to the Marsh study showing the lowest bone density in total vegetarians. Additionally, the animal protein intakes of the Framingham subjects showed no deleterious effect on bone. Furthermore, Heaney suggested that a vegan diet with protein derived equally from grains and legumes could deliver as many millimoles of sulfur per gram of protein as a meat-based diet (see Table 1). Therefore, the presence or absence of sulfur containing amino acids may not thoroughly explain the basic or acidic excess of a food. Heaney suggested that the calcium: protein ratio be considered in determining the body's calcium need.

Soyfoods and Calcium Bioavailability

Soybeans have high calcium content relative to other plants and high fractional absorption of calcium, despite their high content of oxalate and phytate. Both oxalate and phytate are inhibitors of calcium absorption. However, oxalate is a more potent inhibitor than phytate due to the degree of insolubility of the oxalate-calcium complex. Moreover, phytate is the storage form of phosphorus in plants, which lowers the bioavailability of calcium by forming phosphorus-calcium complexes. It is extremely important to note that phytate appears only to substantially reduce calcium absorption in phytate-concentrated wheat bran cereal (35). The following table lists examples of natural sources of calcium and the amounts necessary to equal the calcium contained in one cup of milk. The number of servings required to replace one cup of milk for absorbable calcium are approximately three servings of cooked soybeans, eight servings of pinto beans, ten servings of red beans, and four servings of white beans.

Table 2. Comparison of Other Natural Sources of Calcium to Milk[a]

Food	Serving Size (g)[1]	Calcium Content (mg)[2]	Fractional Absorption (%)[3]	Milk Equivalents (cup)
Milk	240	300	32.1	1.0
Beans				
Pinto	86	44.7	26.7	8.1
Red	172	40.5	24.4	9.7
Soybeans[4]	86	100	31-42	2-3
White	110	113	21.8	3.9
Broccoli	71	35	61.3	4.5
Kale	85	61	49.3	3.2
Spinach	85	115	5.1	16.3
Tofu with calcium	126	258	31.0	1.2

[a] Adapted from Weaver CM et al (36).

[1] Based on half-cup serving size (~85g for green leafy vegetables) except for milk (1 cup or 240 mL).

[2] Average for beans (except for soybeans) and broccoli processed in different ways, which were analyzed in the Weaver lab at Purdue University.

[3] Adjusted for load by using the equation for milk [fractional absorption = 0.889-0.0964 ln load (37)] then adjusted for the ratio of calcium absorption of the test food relative to milk tested at the same load, the absorptive index. The absorptive index was taken from the literature for beans (38), broccoli and kale (39) and tofu (40).

[4] Fractional absorption and milk equivalents are based on field soybeans with variable ranges of phytate content (35).

Some calcium-fortified foods have fractional calcium absorption values – in other words, the amount of calcium that can be absorbed from these foods – that are similar to the calcium absorption value of milk (36). For example, Table 2 shows that the fractional absorption of calcium-set tofu is 31% relative to 32.1% for milk and the milk equivalency of calcium-set tofu is 1.2 servings. Furthermore, in a rat study conducted by Poneros and Erdman, the bioavailability of calcium in calcium-fortified tofu did not differ from the bioavailability of calcium from cheese, calcium carbonate, or nonfat dry milk (41).

In a human study, Heaney et al. found that the calcium absorption efficiency of tri-calcium phosphate (TCP) fortified soymilk was only 75 percent the calcium absorption efficiency of cow's milk (42). However, the authors noted that the results cannot be generalized to all soymilk products due to use of different calcium salts. Moreover, due to results of unpublished experiments conducted with TCP in a candy syrup matrix and yogurt, the authors suggested that the lower calcium absorption efficiency of the TCP fortified soymilk was due to "antiabsorbers" or inhibitors of absorption. Specifically, the fractional calcium absorption of the TCP fortified candy syrup matrix and the yogurt were not statistically different from the fractional calcium absorption of cow's milk. In addition, Heaney et al. calculated that fortification of 500-mg/serving with TCP would result in the same amount of calcium absorbed from soymilk as in a serving of cow's milk with 300-mg calcium. Currently available calcium-fortified soymilk may contain anywhere from 80 to 500-mg/serving of various calcium fortificants.

Soy based meat products, calcium fortified soy cheese, soy yogurts and ice creams, and soynut butter as well as soymilk are most likely more conveniently substituted for milk and dairy products than cooked soybeans. With the exception of soymilk, the fractional absorption of calcium in these products relative to cow's milk is currently unknown.

Conclusions

Soyfoods not only provide calcium essential to building and maintaining bone, but may also protect against osteoporosis. However, the current understanding of the role of soy in bone health is still in its infancy. We have much more to learn about which compounds in soy protein are bioactive and at what dose, whether soy proteins have a bone protective effect and the mode of action on the bone tissue. Long-term randomized controlled trials are necessary to determine the role of soy protein and soy isoflavones on bone mineral density and fracture incidence.

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