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REVIEW

Soy Isoflavones and Osteoporotic Bone Loss: A Review with an Emphasis on Modulation of Bone Remodeling

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ABSTRACT Osteoporosis is an age-related disorder that affects both women and men, although estrogen deficiency induced by menopause accelerates bone loss in older women. As the demographic shifts to a more aged population, a growing number of men and women will be afflicted with osteoporosis. Since the current drug therapies available have multiple side effects, including increased risk of developing certain types of cancer or complications, a search for potential nonpharmacologic alternative therapies for osteoporosis is of prime interest. Soy isoflavones (SI) have demonstrated potential bone-specific effects in a number of studies. This article provides a systematic review of studies on osteoporotic bone loss in relation to SI intake from diet or supplements to comprehensively explain how SI affect the modulation of bone remodeling. Evidence from epidemiologic studies supports that dietary SI attenuate menopause-induced osteoporotic bone loss by decreasing bone resorption and stimulating bone formation. Other studies have also illustrated that bone site-specific trophic and synergistic effects combined with exercise intervention might contribute to improve the bioavailability of SI or strengthen the bone-specific effects. To date, however, the effects of dietary SI on osteoporotic bone loss remain inconclusive, and study results vary from study to study. The current review will discuss the potential factors that result in the conflicting outcomes of these studies, including dosages, intervention materials, study duration, race, and genetic differences. Further well-designed studies are needed to fully understand the underlying mechanism and evaluate the effects of SI on osteoporosis in humans.

KEY WORDS: • *bone loss* • *bone remodeling* • *osteoclast* • *osteoporosis* • *soy isoflavones*

INTRODUCTION

Osteoporosis is a disease characterized by low bone mass and deterioration in the microarchitecture of bone, resulting in increased risk of bone fragility and fracture.[1] Osteoporosis is the primary cause of morbidity and hospitalization among adults older than 50 years in the United States.[2] Approximately 10 million adults older than 50 years are estimated to have osteoporosis, and an additional 34 million adults are at risk for osteoporosis.[3] It has been reported that $\sim$2 million fractures per year are caused by osteoporosis,[2] and nationwide, the annual medical costs are roughly $19 billion.[3] Without appropriate intervention strategies, the incident rate of osteoporosis will increase threefold for the next 25 years because of the increase in the aging population. Although the challenge is huge for medical care, osteoporosis is a preventable and potentially manageable disease.[4]

Type I osteoporosis (primary osteoporosis) is characterized by trabecular bone demineralization, which mostly occurs in postmenopausal women (50–65 years old) mainly because of reduced estrogen production after menopause. Type II osteoporosis, an age-related bone loss, attacks both men and women older than 70–75 years because of slow loss of bone cells, especially osteoblast cells.[2] According to the U.S. 2013 Clinician's Guide to Prevention and Treatment of Osteoporosis, the diagnosis of osteoporosis is based on the measurement of bone mineral density (BMD) by dual-energy X-ray absorptiometry.[5]

Clinically, estrogen or estrogen replacement therapy (ERT) has been commonly used for peri- or postmenopausal women to attenuate bone loss by decreasing or slowing bone turnover rates. However, ERT-related side effects, such as vaginal bleeding, increased risk of breast cancer, uterine cancer, and cardiovascular events, have been reported.[6] Thus, dietary and herbal approaches, such as food supplements and herbal medicines, have been introduced as alternative approaches to ERT.

A wide range of interest has focused on the topic of soy and health benefits, especially the role of soy in health promotion and chronic disease prevention and treatment. Various nutritional supplements have been produced from soybeans on the market, such as vitamin E, lecithin, and isoflavones.[7] While protein, soybean oil, and carbohydrates

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are the main components of soy, soy foods also contain varying concentrations of phytoestrogens called isoflavones.[7]

This literature review covers the bone preventive effects of natural dietary soy isoflavones (SI) in human and animal studies and attempts to explain the underlying mechanisms on how they affect the bone health in peri-/postmenopausal women. Studies were conducted through the U.S. National Library of Medicine National Institutes of Health online databases PubMed and Scopus. Papers were identified through two searching methods to determine the relationship between SI and postmenopausal bone loss: Mesh (''Isoflavones'' [Mesh]) AND ''Bone and Bones'' [Mesh] and key words, including soy isoflavones, soy phytoestrogen, bone loss, osteoporosis, fracture, and bone health. Scopus was used as a secondary search engine to ensure covering all studies. An extensive period of publication was included until June 2014).

BONE REMODELING AND OSTEOPOROTIC BONE LOSS

The skeleton is constantly being remodeled in response to changes in mechanical load, serum calcium, and microdamage. Bone remodeling involves coordinated actions of osteoclasts to remove bone matrix through resorption of old bone followed by osteoblasts creating new bone through the secretion and mineralization of new bone matrix.[8,9] Both processes are important to the maintenance of bone volume and structure.[10,11] Signaling from the osteoblasts or osteocytes triggers the remodeling process and activates osteoclasts digging the cavities into bones. At the same time, osteoblasts arising from local mesenchymal stem cells start assembling at the bottom of the cavities. Once the resorbed lacunar pit is filled with new osteoid, osteoblasts become flattened and less active. Eventually, the newly remodeled bone surface is lined by flat lining cells. A majority of osteoclasts die by apoptosis during the progression of formation, while some of the osteoblasts are entombed within the matrix as osteocytes (terminally differentiated cells).[12]

It has been known that bone formation outweighs bone resorption in the puberty stage; controversially, bone resorption occurs at a higher rate in full adulthood.[13] There is about 0.5–1% loss in bone mass every year once peak bone mass is reached.[13] Because of the fact that bone remodeling is orchestrated by various cytokines and hormones, which help maintain bone homeostasis,[9] this gradual bone loss shows no significant effect on the development of metabolic bone disease. Until the balance is broken by the sharp loss of hormone in naturally occurring menopause or ovariectomy operation in females, the risk of osteoporosis may increase. Epidemiologic studies have showed that after menopause, the rapid bone loss in spongy or trabecular bone of vertebrae, pelvis, and distal forearm highly increases the risk of developing osteoporosis.[14]

SI AND BONE HEALTH

Epidemiologic studies have found that Asian women have a lower hip fracture incidence in elderly compared to Caucasian women.[15,16] Researchers further found that the consumption of soybean and soy-based products was much higher among Asians than that among Caucasians,[16] which could potentially lower the bone loss rate and decrease the risk of fracture, and SI, naturally occurring plant compounds structurally similar to mammalian estrogens, are the major phytoestrogens contained in soybean and soy-based products.[17,18]

They can act as an antiresorptive and bone-sparing agent in preventing osteoporosis. Daidzin (DAN) and genistin (GEN) as glycosides and their corresponding aglycone forms (daidzein and genistein) are the major isoflavones in soy. The phenolic rings in their structures are critical structural elements to bind estrogen receptors (ERs) and exert estrogen-like effects.[19] Studies by Yu *et al.*[20] and Tang *et al.*[21] have ascertained that both GEN and DAN have the ability to modulate bone remodeling by directly regulating gene expression of target ERs in human osteoblastic cells.

In addition to the direct estrogenic/antiestrogenic effects, SI have also been reported to have a number of biologic effects, including antioxidant effects, induction of cell differentiation and apoptosis, and inhibition of tyrosine kinase and topoisomerases.[22] GEN has been shown to possess antioxidant, antiproliferative, estrogenic, and immune-modulating effects.[23] Its property of antidiabetic, hypolipidemic, and anti-inflammatory effects may reduce risk of cardiovascular disease, while its antioxidant properties make it work as a chemopreventive agent in preventing the development of breast cancer.[24] These effects may lead to a modestly beneficial effect on maintaining or preventing bone loss.[25]

To date, the ability of SI on reducing bone turnover has been demonstrated through inhibiting bone resorption and stimulating bone formation in several studies.[26–28] GEN was found retarding bone resorption by decreasing the viability of 1,25-dihyroxyvitamin D-induced osteoclasts at 10^{-8} M.[29] Dietary soy also can function through increasing or sustaining the elevated bone formation rate,[30–32] which is different from the effect of estrogen on preservation of estrogen deficiency-related bone loss. Studies found that the positive effects of SI were achieved through enhanced bone formation by increasing serum osteocalcin (OC, a bone formation marker)[30] concentration, femoral insulin-like growth factor 1 (IGF-I) mRNA transcription,[31] and serum alkaline phosphatase (ALP, a bone formation marker) activity.[32] Instead of only slowing bone resorption, SI may also help reduce bone turnover rate through enhanced bone formation. Although the conclusions among studies are varied, in general, bone-related protective effects of SI are mainly through stimulating bone formation while inhibiting bone resorption.

A comprehensive cDNA microarray study conducted by Pie *et al.*[33] demonstrated a better explanation of how SI maintain the bone homeostasis through gene expression. They ascertained that GEN could upregulate 38 (*e.g.*, IGF-1 and ER1) and downregulate 18 (*e.g.*, interleukin [IL]-6, IL-1β, and MMP13) bone-related genes. These genes participate in the regulation of bone remodeling process through either stimulating or suppressing the expression. These findings are interesting with regard to the interaction between SI and bone in the regulation of bone remodeling. The regulatory

nature of SI on inflammatory cytokines has been found in ovariectomized (OVX) rats fed with SI: SI decrease bone turnover by changing IL-6 level.[34]

In a longitudinal study, soy consumption was found to decrease serum tumor necrosis factor (TNF)-α level in postmenopausal women.[22] Using multiple regression modeling, a 1-year clinical intervention study with postmenopausal women concluded that the small change in the inflammation markers had important contributions to the percent change in bone mineral content (BMC) or BMD in a variety of bone sites.[35] *In vitro* study on the effects of individual soybean SI (GEN and DAN) on TNF-α-induced apoptosis and the production of local factors in osteoblastic cells further prove that the function of osteoblasts can be promoted by decreasing TNF-α-induced IL-6 and prostaglandin E2 levels.[36] Hence, reducing inflammatory cytokines may play a role in reducing bone turnover rate.

SI may also promote calcium absorption in a manner analogous to that of estrogen without exerting uterotrophic effect.[37,38] In contrary to estrogen, which mediates osteoclasts to release calcium from bone, Lien *et al.* reported that bone ash and calcium contents were higher in SI-treated OVX rats.[39] The *in vitro* study conducted by the same group found that SI-treated osteoprogenitor cells had a higher viability, ALP activity, OC, and calcium content.[39] It has also been shown that GEN can decrease bone turnover by stimulation of cadmium (Cd) excretion while inhibiting calcium excretion from bone in Cd/OVX rats.[40]

Interestingly, there exists different dose responses between calcium concentration and a gradual increased dose of supplementary equol (a metabolite of SI) in OVX rats.[41] The tibia of these equol-fed OVX rats showed an inverse relationship in calcium concentration and BMD, whereas the femoral neck showed a positive relationship. Therefore, the effects of SI on maintaining calcium homeostasis can be concluded as decreasing calcium excretion and increasing calcium conservation/absorption. However, sometimes because of differences between bone types (cortical or trabecular), bone turnover mechanisms may differ from each bone site. The differences also make it hard to compare results from studies using various bone sites.

Today, numerous studies are focusing on the potentially beneficial effects of SI in the bone loss, especially on osteoporosis in postmenopausal women. However, the results from those studies were not quite consistent, mainly because of the variation in the study designs (*e.g.*, intervention materials, dosage, study duration, and endpoint measurement). Other factors, including race, age, and equol production status, as covariates may also affect the result. Some studies further explored the synergistic effects of dietary/supplemental SI and exercise, which might help achieve maximum bone-preserving effects.

Dosages

The biphasic effect of GEN on bone tissues was demonstrated in an *in vivo* study with OVX rats: it had a similar effect as estrogen on bone tissues in a lower dose (0.5 mg/day), while it was less effective in a higher dose (5.0 mg/day), with the potential introduction of adverse effects.[42] This effect could be interpreted through the balance between osteogenesis and adipogenesis: osteogenesis is stimulated by the low dose of DAN, while adipogenesis responded to the higher dose.[43]

Kim and Lee compared SI supplemental treatments (80 or 160 μg/g diet) with estrogen therapy in OVX rats and found 80 μg/g is as effective as estrogen therapy in preventing osteoporotic bone loss.[44] Another study reported that 60 μg/g bw/day SI can effectively mitigate OVX-induced osteoporosis in middle-aged OVX mice compared to the 30 μg/g bw/day.[45] As mentioned earlier, the dosage used in the study can substantially affect the study outcomes; this unclear effective dose also leads to a lot of variances in both animal and human studies (Tables 1 and 2).

In clinical trials, some studies showed that the effective dose was ~40 mg/day, while other studies showed 110 mg/day was the optimal dose. Ye *et al.* proposed that a low-dose treatment (40 mg/day) had no significant effect on BMD in early postmenopausal women,[46] while another series of observational studies have showed that a habitual daily intake of 30–40 mg/day was associated with better peak bone mass in young females[47] and potentially maintains better bone mass in postmenopausal women.

Without controlling dietary soy product intake, a 4-week study with 61.8 mg/day SI in Japanese women showed more significant effects on bone metabolism by decreased bone resorption.[48] This change compared to other studies using a similar dose without significant outcomes could be because of the habitual daily soy food intake in Japan. The actual SI dosage used in this study should be higher than the reported. Moreover, the work of Ye *et al.* also found a linear dose-dependent beneficial effect on bone loss at dosages of 84 and 126 mg/day.[46] A significant bone protective effect was ascertained with 126 mg/day SI intake by retarding bone loss at the femoral neck. Therefore, a threshold may exist to regulate how SI affects bone metabolism. However, because of the different study designs, such as the intervention materials and study duration, it was difficult to conclude what the most effective dosage would be.

Intervention materials

To date, the most frequently used products were soy protein enriched with SI, isolated SI extract supplements, and purified single components (such as GEN and DAN). Supplements of isolated SI extracts used in studies were usually constructed based on different formulas (percent content of DAN and GEN). However, other functional contents (such as glycitein) may also be included and make it hard to compare the effects of single SI extract with SI under soy protein matrix or other formats. Therefore, SI were discussed in this review in general.

Genistein versus daidzein. Although GEN and DAN are both members of the SI family, they may have different mechanisms or effects on the bone health. The study by Picherit *et al.* indicated that DAN was more efficient in preventing OVX-induced bone loss compared with GEN.[49] Comparing three SI (GEN, DAN, and glycitein) in OVX rats, Uesugi *et al.*[50] illustrated that DAN and glycitein

Table 1. Summary of Animal Studies on Preventive Effects of Soy Isoflavones on Bone Loss

Study	Subjects	Duration	Intervention	Outcomes	
				BMD/BMC	Bone turnover markers
Anderson *et al.*[42]	OVX and lactating SD rats ($n=30$)	2 weeks	SH versus OVX (G [0.5 mg/day], G [1.6 mg/day], G [5.0 mg/day], C, E)	G (0.5 mg/day): femur BMD (+)	N/A
Arjmandi *et al.*[31]	95-day female SD rats ($n=72$)	65 days	SH versus OVX (C, SP)	BMD (NS)	Serum ALP, urinary Hyp (NS)
Picherit *et al.*[49]	12-month female Wistar rats ($n=65$)	3 months	SH versus OVX (G [10 μg/g bw/day], D [10 μg/g bw/day], E)	D: BMD (+); G: BMD (NS)	D: plasma OC (–); G and D: urinary Dpd (–)
Picherit *et al.*[88]	7-month female Wistar rats ($n=55$)	84 days	SH versus OVX (C, SI at 20, 40, 80 μg/g bw/day)	BMD (NS)	SI: serum OC (–); SI (80): urinary Dpd (–)
Uesugi *et al.*[50]	11-week female SD rats ($n=36$)	4 weeks	SH versus OVX (C, Gly [100 μg/g bw/day], D [25 μg/g bw/day], G [50 μg/g bw/day], E)	N/A	D and Gly: urinary Dpd (–)
Mihalache *et al.*[32]	9-month female rats ($n=27$)	9 weeks	SH versus OVX (C, SP [7%])	Femur and tibia: BMD (+)	SP: ALP (+)
Blum *et al.*[30]	11-month female SD rats ($n=44$)	3 months	SH (C, SP) versus OVX (C, SP)	Femur BMD (+)	Bone formation rate (+)
Paik *et al.*[40]	4-week female Wistar rats ($n=45$)	8 weeks	SH versus OVX (C, CdCl, G [10 μg/g bw/day], E + CdCl)	BMD (NS)	G: serum OC, Ca (–)
Register *et al.*[105]	OVX female cynomolgus macaques ($n=181$)	3 years	C, E, SPE	BMD (NS)	SPE: ALP, calcium, CTX (–)
Mathey *et al.*[106]	3-month female Wistar rats ($n=12$)	90 days	SH versus OVX (IF [0, 10, 20, 40, 80 μg/g bw/day]; IF [0, 10, 20, 40, 80 μg/g bw/day] + FOS)	FOS: BMD (+)	IFs: plasma OC (NS), urinary Dpd (+)
Wu *et al.*[100]	8-week female mice ($n=48$)	6 weeks	SH versus OVX (C, IF (160 μg/g bw/day), EX, IF (160 μg/g bw/day) + EX, E)	IF, EX, IF + EX, E: BMD (+)	N/A
Fonseca and Ward[107]	8-week mice ($n=84$)	12 weeks	SH versus OVX (C, HCa, HD [200 μg/g diet], HDCa, LD [100 μg/g diet], LDCa)	HD, HDCa: BMD (+)	N/A
Bahr *et al.*[57]	3-month female SD rats ($n=56$)	12 weeks	SH versus (C, SP [100 μg/g diet], SP [200 μg/g diet], IF [17.2 μg/g diet], IF [34.4 μg/g diet])	Femur and tibia: BMD (NS)	Urinary Dpd (NS)
Nakai *et al.*[56]	3-month female SD rats ($n=50$)	12 weeks	C, SP (100 μg/g diet), SP (200 μg/g diet), IF (17.2 μg/g diet), IF (34.4 μg/g diet)	BMD (NS)	SP and IF: urinary Dpd (–)
Nakai *et al.*[108]	3-month Fischer 344 rats ($n=57$)	14 weeks	C, low SP (100 μg/g diet), high SP (200 μg/g diet), low IF (17.2 μg/g diet), high IF (34.4 μg/g diet)	Femur BMD (NS); low IF: lumbar BMD (+)	High SP: urinary Dpd (–)
Erlandsson *et al.*[51]	6-week female mice ($n=40$)	32 weeks	SH versus OVX (C, E, G [50 μg/g bw/day])	BMD (+)	N/A
Breitman *et al.*[109]	90-day female SD rats ($n=50$)	8 weeks	SH versus OVX (C, HCa, SP [20%], SP [20%] + HCa)	SP + HCa: femur BMD (NS), lumbar spine BMD (+)	N/A
Watkins *et al.*[110]	2-month female SD rats ($n=50$)	12 months	N6 – IF (0.03 mg/g), NF + IF (3.43 mg/g SP), N3 – IF (0.03 mg/g SP), N3 + IF (3.43 mg/g SP)	N3 + IF: tibia BMC (+)	N3 + IF: ICTP (–); urinary Dpd, OC, BAP (NS)

(*continued*)

TABLE 1. (CONTINUED)

Study	Subjects	Duration	Intervention	Outcomes	
				BMD/BMC	Bone turnover markers
Gallo *et al.*[34]	2-month female SD rats ($n=60$)	6 weeks	SH versus OVX (C, SE [50 μg/g bw/day], SE [100 μg/g bw/day], E)	SE (100): BMD (+)	SE (100): serum OC, urinary Dpd (−)
Kim and Lee[44]	9-week female OVX SD rats ($n=49$)	6 weeks	SH versus OVX (SI at 0, 80, 160 μg/g diet) versus OVX (E + SI at 0, 80, 160 μg/g diet)	SI (80): BMC (+); SI (160): BMC (NS)	Serum ALP, TRAP, Ca (NS); urinary Hyp (NS)
Devareddy *et al.*[55]	9-month female SD rats ($n=78$)	120 days	SH versus OVX (C, E, soy − IF, soy + IF [7.1 mg IF/g·SP])	Soy: tibia BMC, BMD (+); soy + IF: Tb.N (+), Tb.Sp (−)	N/A
Figard *et al.*[104]	12-week female OVX SD rats ($n=48$)	8 weeks	C, SP (0.2 μg/g diet), C + SW, SP + SW	N/A	SPs: plasma OC (−), urinary Dpd (−), plasma Ca (+)
Devareddy *et al.*[111]	9-month female SD rats ($n=63$)	4 months	SH versus OVX (C, SP, FOS, SP + FOS)	FOS: BMD (+); SP + FOS: Tb.Th (+), Tb.Sp (−)	N/A
Lien *et al.*[39]	11-week SD female rats ($n=20$)	3 months	SH versus OVX (C, SAI [18.33 μg/g bw/day])	BMC (+)	N/A
Cheng *et al.*[112]	6-month SD female rats ($n=50$)	12 weeks	SH versus OVX (Ca, IF [37.95 μg/g diet], Ca, Ca + IF)	Ca + IF: femur BMD (+)	Ca + IF: IGF-1 mRNA (−)
Mathey *et al.*[95]	3-month female Wistar rats ($n=70$)	3 months	SH versus OVX (C, G [10 μg/g bw/day], D [10 μg/g bw/day], equol [10 μg/g bw/day], D [10 μg/g bw/day] + FOS, D [10 μg/g bw/day] + L)	G, D, equol: femur BMD (+); Note: FOS and L enhance bone protective effect of D	Plasma OC, urinary Dpd (NS)
Shiguemoto *et al.*[101]	13-week female Wistar rats ($n=56$)	12 weeks	SH versus OVX (C, SY, REX, SY + REX)	Sys: femur and tibia BMD (+)	SY: serum ALP (+)
Ward and Fonseca[113]	6-month CD-1 mice ($n=60$)	12 weeks	SH versus OVX (SI [D + G, 250 μg/g diet], FO, SI + FO)	SI: femur BMD (+); FOs: lumbar vertebra BMD (+)	SI: serum OC (NS)
Om *et al.*[114]	4-week female Cd-exposed female Wistar rats ($n=45$)	8 weeks	SH versus OVX ($CdCl_2$, Cd-D [10 μg/g bw/day], Cd-E [10 μg/g bw/day])	BMD (NS)	Cd-D: serum OC (−)
Rachon *et al.*[96]	3-month female OVX SD rats ($n=28$)	6 weeks	C, E, equol (400 μg/g diet)	BMD (+)	Plasma OC, CTX (NS)
Sehmisch *et al.*[115]	4-month OVX SD rats ($n=88$)	12 weeks	C, E, G, RES, 8PN	BMD (NS)	N/A
Seidlová-Wuttke *et al.*[116]	Young, middle-aged, and aged female rats ($n=20$)		Soy− versus Soy+	N/A	Soy+: serum OC (NS), serum crosslaps (+)
Kim *et al.*[45]	12-month OVX mice ($n=40$)	4 months	SI (30 μg/g bw/day),SI (60 μg/g bw/day), E	SI (60 mg): BMD (+)	SI: ALP (+), TRAP (−)
Legette *et al.*[41]	6-month female SD rats ($n=78$)	8 weeks	SH versus OVX (equol at 0, 50, 100, 200 μg/g diet)	BMD (NS)	Femur and tibia: Ca (+)
Zhang *et al.*[54]	12-week female OVX mice ($n=56$)	5 weeks	C, G, Novasoy, E	Novasoy: proximal tibial metaphysis trabecular bone volume, Tb.Sp (+)	G: mRNA expression of RANKL (−); Novasoy: ALP (+)
Jeon *et al.*[117]	6-week female SD rats ($n=30$)	19 weeks	SH versus OVX (C, IF, IF + Vit + Ca)	IF and IF + Vit + Ca: BMD (+)	IFs: BALP, ALP(+); urinary Dpd, Hyp (−)

(*continued*)

Table 1. (Continued)

Study	Subjects	Duration	Intervention	Outcomes	
				BMD/BMC	Bone turnover markers
Tezval *et al.*[118]	3-month female OVX SD rats ($n=48$)	5 weeks	C versus G (12.7 mg/day), equol (4.65 mg/day), E	Equol: Tb.Ar, Tb.N (+)	N/A
Byun and Lee[119]	7-week female OVX SD rats ($n=47$)	10 weeks	C, yellow soybean, black soybean, sword bean	Femur, lumbar spine: BMD, BMC (+)	OC (–), urinary Dpd (–)
Hooshmand *et al.*[120]	90-day female SD rats ($n=48$)	50 days	SH versus OVX (C, G [5 μg/g bw/day], G+FOS)	G: whole-body, lumbar, femur BMD (+)	G: ALP (–); G and G+FOS: OC (NS)
Sehmisch *et al.*[94]	3-month OVX rats ($n=48$)	35 days	C, E, G (1 g/kg diet), equol (0.4 g/kg diet)	Trabecular bone volume (NS)	G and equol: OC, crosslaps (NS)
Komrakova *et al.*[121]	3-month female SD rats ($n=48$)	5 and 10 weeks	Soy– versus Soy+ (4-MBC [200 μg/g bw/day], D [50 μg/g bw/day]), E	Soy +4-MBC: BMD (+); soy+ D: BMD (NS)	Serum OC, ALP (NS)
Chiang *et al.*[122]	3-month female mice ($n=20$)	6 weeks	C versus soy skim milk (NTU101F, NTU102F)	BMD (NS); NTU101F and NTU102F: trabecular bone volume (+)	NTU101: ALP (NS), ACP (–)
Florencio-Silva *et al.*[102]	6-month female Wistar rats ($n=40$)	90 days	SH versus OVX (C, IF [200 μg/g bw/day], vibration, IF [200 μg/g bw/day]+vibration]	IF: trabecular bone volume (NS)	N/A
Nishide *et al.*[123]	12-week female ddY mice ($n=30$)	2 weeks	SH, OVX (C, equol [0.06% S-equol])	Femur distal region: BMD (+)	Equol: mRNA expression of inflammatory-, osteoclastogenesis- and adipogenesis-related gene (-)
Turner *et al.*[124]	3-, 12-, and 14-month female Long–Evans rats ($n=89$)	4 months	C, G (485 μg/day), G (970 μg/day)	BMD (NS)	N/A
Srivastava *et al.*[125]	21- to 22-day female SD rats ($n=50$)	12-week baseline +12-week treatment	SH+Ve, OVX+Ve, OVX+E, OVX+Ve+SE (50 μg/g bw/day), OVX+Ve+SE (100 μg/g bw/day)	SE (100): Cs.Th, B.Ar, T.Ar, T.Pm (+)	SE (100): urinary CTX (–)

Outcome measures (BMD/BMC, bone turnover markers) refer to the results from intervention treatments with soy isoflavones.

+, improvement/increased; –, decreased; NS, not significant; ALP, total alkaline phosphatase; B.Ar, bone area; bw, body weight; BMD, bone mineral density; BMC, bone mineral content; C, control diet; Cd, cadmium; Cs.Th, cortical thickness; CTX, cross-linked C-telopeptide of type I collagen; D, daidzein; Dps, deoxypyridinoline; E, estrogen; EX, exercise; FO, fish oil; FOS, fructooligosaccharides; G, genistein; Gly, glycitein; Hyp, hydroxyproline; ICTP, pyridinoline cross-linked carboxyterminal telopeptide of type I collagen; IF, isoflavone; IGF-1, insulin-like growth factor-1; L, *Lactobacillus casei*; N/A, not applicable; N3, *n*-3 polyunsaturated fatty acid; N6, *n*-6 polyunsaturated fatty acid; NTU101F, soy skim milk fermented by *Lactobacillus paracasei* subsp. Paracasei NTU101; NTU102F, soy skim milk fermented by *L. plantarum* NTU102; OC, osteocalcin; 8PN, 8-prenylnaringenin; RES, resveratrol; REX, resistive exercise; SAI, soy aglycone isoflavone; SD, Sprague-Dawley; SE, soy extract; SI, soy isoflavones; SP, soy protein; SPE, soy phytoestrogen; SPI, soy protein isoflavones; SW, swimming; T.Ar, periosteal area; Tb.N, trabecular number; T.Pm, periosteal perimeter; TRAP, tartrate-resistant acid phosphatase; Tb.Sp, trabecular separation; Vit, vitamin; Ve, vehicle.

Table 2. Summary of Human Intervention Studies on Prevention Effects of Soy Isoflavones on Bone Loss

Study	Subjects	Duration	Intervention (dose)	Outcomes	
				BMD/BMC	Bone turnover markers
Cross-sectional studies					
Somekawa *et al.*[59]	Japanese post-M (44–80 years, $n=478$)		Soy consumption (54.3 mg/day IF)	Lumbar spine: BMD (+)	N/A
Kritz-Silverstein *et al.*[60]	Post-M (45–74 years, >2 YSM, $n=208$)		FFQ (G, D, and IF intake)	High IF intake: spinal BMD (+)	NTX (–); BAP, Pyr (NS)
Nagata *et al.*[126]	Japanese post-M (>1 YSM, $n=87$)		FFQ (soy product and IF intake)	BMD (NS)	ALP (NS)
Ho *et al.*[47]	Chinese post-M (<12 YSM, $n=454$)		FFQ (SP intake, 9.6–76.9 g/day)	Spine, hip, whole body: BMD (+)	N/A
Prospective observational studies					
Song *et al.*[89]	Korean women (20–26 years, $n=34$)	2 years	24-h recalls: (soybean and soy product intake)	FN and WT: BMD (+); lumbar spine and FT: BMD (NS)	N/A
Koh *et al.*[127]	Chinese women and men (45–74 years, $n=63,257$)	5 years	FFQ: tofu equivalents, SP (4.7–7.6 g/day), SI (9.8–15.4 g/day) intake	N/A; Note: fracture risk: 21%–36% (–)	N/A
Prospective intervention studies					
Crossover studies					
Dalais *et al.*[69]	Post-M (45–65 years, $n=52$)	12 weeks	Soy/linseed diet (high phytoestrogen) versus wheat diet (low phytoestrogen)	BMD (NS)	N/A
Wangen *et al.*[128]	Pre-M (21.8–31.5 years, $n=14$); post-M (51.2–63 years, $n=17$)	3 months	SP (8 mg IF/day), SP (65 mg IF/day), SP (130 mg IF/day)	N/A	Post-M: BAP (–), IGF-I and IGFBP3 (–)
Harkness *et al.*[129]	Post-M (>8 YSM, $n=19$)	6 months	SI (110 mg/day) versus C	Hip and spine: BMD/BMC (NS)	Serum OC (–)
Roughead *et al.*[72]	Post-M (50–75 years, $n=13$)	7 weeks	SP versus C	BMD (NS)	Ca retention, Hyp (NS)
Cheong *et al.*[130]	Post-M (>6 YSM, $n=13$)	50 days	SP versus SP (97.5 mg IF/day), SP (135.5 mg IF/day)	BMD (NS)	Serum BAP, OC, PTH, serum 25(OH)D, serum $1,25(OH)_2D$ (NS); urinary NTX (NS)
Two-arm parallel intervention studies					
Potter *et al.*[58]	Post-M (>1 YSM, $n=66$)	6 months	SP (56 mg/day IF), SP (90 mg IF/day) versus C	SP (90): BMD (+)	N/A
Uesugi *et al.*[48]	Japanese peri-M (40–62 years, $n=23$)	4 weeks	IF (61.8 mg/day) versus placebo	BMD (NS)	Serum OC (NS); urinary Dpd, Hyp (–)
Dalais *et al.*[131]	Post-M (50–75 years, $n=106$)	3 months	SP (118 mg IF/day) versus placebo	N/A	Urinary IF (+), Dpd (NS)
Chen *et al.*[62]	Asian post-M (48–62 years, $n=203$)	1 year	IF (40 mg/day), IF (80 mg/day) versus placebo	IF (80 mg/day): hip and trochanter BMC (+)	N/A
Mori *et al.*[64]	Japanese pre-M/post-M (40–60 years, $n=81$)	4 weeks	IF (40 mg/day) versus placebo	N/A	IF: urinary Dpd (–), BGP (NS)
Kreijkamp-Kaspers *et al.*[71]	Netherlandish post-M (60–75 years, $n=202$)	12 months	IF (99 mg/day) versus placebo	BMD (NS)	BAP (NS)
Chen *et al.*[63]	Post-M (48–62 years, $n=203$)	1 year	IF (40 mg/day), IF (80 mg/day) versus placebo	Hip and trochanter: BMC (+)	N/A
Mori *et al.*[132]	Japanese pre-M/post-M (40–63 years, $n=81$)	24 weeks	IF (100 mg/day) versus placebo	BMD (+)	Urinary Dpd (–), BGP (NS)
Lydeking-Olsen[133]	U.S. white post-M, (YSM >1, $n=107$)	2 years	Soy milk (76 mg IF/day), TPD, TPD+ soy milk versus placebo	FN: BMD (NS); lumbar: BMD (+)	PINP, ICTP (NS)
Roudsari *et al.*[134]	Peri-M (45–64 years, $n=15$)	12 weeks	SP (35 g/day)	N/A	Urinary Dpd (–), ALP (+); CTX, OC, IGFBP3 (NS)

(*continued*)

TABLE 2. (CONTINUED)

Study	Subjects	Duration	Intervention (dose)	Outcomes	
				BMD/BMC	Bone turnover markers
Arjmandi *et al.*[135]	Post-M (>65 years, $n=87$)	1 year	SP (60 mg IF/day) versus placebo	BMD (NS)	OC, BAP, IGF-1, ALP (+); IGFBP (NS)
Ye *et al.*[46]	Chinese peri-M (45–60 years, $n=90$)	6 months	IF (84 mg/day), IF (126 mg/day) versus placebo	Lumbar spine and FN: BMD (+)	Urinary Dpd (–); OC, BAP (NS)
Newton *et al.*[64]	Women (50–80 years, $n=22$)	12 months	Soy drink (IF [83 mg/day] versus IF [3 mg/day])	IF (83 mg): spinal BMD (+), hip BMD (NS)	N/A
Huang *et al.*[65]	Taiwanese post-M (45–67 years, $n=43$)	1 year	IF (100 mg/day), IF (200 mg/day) versus placebo	IF (100 mg/day): BMD (+); IF (200 mg/day): BMD (NS)	Urinary NTX (NS); urinary Dpd, serum ALP (+)
Evans *et al.*[73]	Post-M (50–65 years, $n=61$)	9 months	SPI versus MPI; SPI + EX versus SPI – EX	BMD (NS)	SPI: CTX (–), BAP (–); SPI + EX: CTX (–), BAP (NS)
Marini *et al.*[66]	Italian post-M (49–67 years, $n=389$)	24 months	G (54 mg/day) versus placebo	BMD (+)	Urinary Dpd (–), ALP (+), IGF-1 (+), 25-OH-Vit D (+)
Wu *et al.*[91]	Japanese post-M (<5-year YMS, $n=45$)	1 year	IF (75 mg/day) versus placebo; Note: equol producer versus nonequol producer	Equol producer: BMD (+)	N/A
Brink *et al.*[74]	Post-M (50–56 years, $n=237$)	1 year	IF (110 mg/day) versus placebo	BMD (NS)	ALP, PINP, urinary Dpd (NS)
Dong *et al.*[75]	Chinese post-M (45–65 years, $n=93$)	12 months	Ca, Ca + IF (100 mg/day) versus placebo	BMD (NS)	N/A
Radhakrishnan *et al.*[136]	Post-M (>1-year YMS, $n=100$)	6 months	SP (75 mg IF/day) versus placebo	BMD (NS)	N/A
Vupadhyayula *et al.*[76]	Post-M (>55 years, $n=203$)	2 years	SP, SP (90 mg IF/day), MP	BMD (NS)	Serum 25-OH-Vit D, PTH, NTX (NS)
Kenny *et al.*[18]	Post-M (>60 years, $n=131$)	1 year	SP (105 mg IF/day), SP, CP (105 mg IF/day), CP	BMD (NS)	Serum BAP (+), urinary NTX (NS)
Alekel *et al.*[67]	Post-M (45.8–65 years, $n=224$)	3 years	IF (80 mg/day) versus IF (120 mg/day)	IF (120 mg/day): FN BMD (+)	Serum CTX, BAP (NS)
Wong *et al.*[77]	Post-M (40–60 years, $n=403$)	2 years	IF (80 mg/day), IF (120 mg/day) versus placebo	BMD (+)	N/A
Gertz *et al.*[35]	Post-M (45.8–65 years, $n=242$)	1 year	IF (80 mg/day) versus IF (120 mg/day)	IF (120 mg/day): BMD (+)	N/A
Shedd-wise *et al.*[137]	Post-M (46.1–63.1 years, $n=224$)	3 years	Placebo versus IF (80 mg/day), IF (120 mg/day)	BMD (NS)	BAP (NS), CTX (+)
Tousen *et al.*[92]	Japanese post-M (41–62 years, nonequol producer, $n=90$)	1 year	Equol (2 mg/day), equol (6 mg/day), equol (10 mg/day) versus placebo	Equol (10 mg/day): BMD (+)	OC, BAP, NTX (NS); equol (10 mg): urinary Dpd (–)
Zhou *et al.*[138]	Nonsmoking women (18–28 years, $n=63$)	10 weeks	Soy food (36 mg IF/day) versus animal food	N/A	BAP (+), CTX (NS)
Levis *et al.*[78]	Post-M (45–60 years, $n=248$)	2 years	IF (200 mg/day) versus placebo	BMD (NS)	NTX (NS)
Yang *et al.*[139]	Taiwanese post-M (>45 years, $n=130$)	24 weeks	SE (70 mg/day) versus SE (35 mg/day)	N/A	Urinary Dpd, serum BAP (NS)
Tai *et al.*[79]	Taiwanese post-M (45–65 years, $n=431$)	2 years	IF (300 mg/day) versus placebo	BMD (NS)	BAP, NTX (NS)
Garcia-Martin *et al.*[68]	Spanish post-M ($n=99$)	12 months	Milk product (50 mg IF/day) versus placebo	BMD (+)	Serum TRAP and OPG (–) 25-OH-Vit D (+)

Outcome measures (BMD/BMC, bone turnover markers) refer to the results from soy isoflavone intervention treatment.

+, improvement/increased; –, decreased; NS, not significant; ALP, total alkaline phosphatase; BAP, bone-specific alkaline phosphatase; BGP, serum bone gamma-carboxyglutamic acid-containing protein; BMD, bone mineral density; BMC, bone mineral content; C, control diet; CP, control protein; CTX, cross-linked C-telopeptide of type I collagen; Dpd, deoxypyridinoline; FFQ, food frequency questionnaire; FN, femoral neck; FOS, fructooligosaccharides; FT, femoral trochanter; ICTP, pyridinoline cross-linked carboxyterminal telopeptide of type I collagen; IF, isoflavone; IGF-1, insulin-like growth factor-1; IGFBP3, insulin-like growth factor-binding protein 3; MP, milk protein; MPI, milk protein isoflavone; N/A, not applicable; NTX, urinary cross-linked N-telopeptide of type 1 collagen; OC, osteocalcin; OPG, osteoprotegerin; PTH, parathyroid hormone; Pyr, urinary deoxypyridinoline; SE, soy extract; SPI, soy protein isoflavones; SSI, strength–strain index; SY, soy yogurt; TPD, transdermal progesterone; TRAP, tartrate-resistant acid phosphatase; YSM, years since menopause; PINP, amino-terminal procollagen propeptide of type I collagen; Vit, vitamin; WT, Ward's triangle.

not only prevented uterine atrophy but also decreased the urinary concentration of pyridinoline and deoxypyridinoline (Dpd). They speculated that DAN or glycitein functions through suppressing bone turnover, while GEN might have a different mechanism. Subsequently, Erlandsson *et al.*[51] revealed that GEN could antagonize ERs in bone to further increase BMD in OVX mice.

Soy protein versus soy isoflavone extracts. Most of the SI studies were using supplements or extracts as their source of SI. However, the extraction process may alter or modify the soy protein and affect its biologic activity. Recent epidemiologic, isotopic, and meta-analysis studies suggested that dietary protein works synergistically with calcium by improving calcium retention and bone metabolism.[52] The matrix of soy protein-enriched SI may improve the bioavailability and biologic efficacy of SI and benefit the bone formation by improving the calcium absorption from lumen or calcium conservation.[53] A study compared GEN-contained diets and Novasoy, a commercial SI-enriched product containing 40% SI and 60% other naturally occurring soy proteins, and found that Novasoy was more effective than purified GEN in improving tibial trabecular bone quality of OVX mice.[54] A similar result was also found in the study by Devareddy *et al.*, where soy protein-enriched SI positively affected tibial architectural properties in the OVX rat model, including trabecular thickness, trabecular separation, and trabecular number.[55]

Furthermore, OVX rats fed with soy protein had a lower body weight and Dpd concentration,[56] whereas those fed with soy protein enriched with a high-dose SI showed statistically significant positive change in bone mass and turnover markers.[57] Thus, soy protein might enhance the ability of SI by transforming them into a more potent beneficial effective form (*e.g.*, equol). Interestingly, in a clinical trial, Kenny *et al.* conducted a 1-year study on 131 postmenopausal women and proposed that there might be a negative correlation between total dietary protein and bone turnover markers: protein intake suppressed the skeletal turnover.[18]

Intervention duration

Table 2 lists studies on humans in response to the effect of SI. Some studies showed significant prevention in bone loss (BMD/BMC) over the duration of the studies[35,46,47,58–68]; others did not prove to have significant effects.[18,69–79] Bone remodeling is a slow process. It normally requires 6–18 months to reach a new equilibrium, and the time required to complete each cycle may be increased with age.[80] As shown in this table, in general, most of the studies with duration longer than 6 months had comparably significant effects. Nevertheless, a 6-month study with a higher dose might have a better protective effect than a 1- or 2-year study with a lower dose.[46,74,75,77] Combined with the biphasic effect of SI, there might be no effect on preserving bone loss in long-term studies when the dose was too high (>200 mg/day).[78,79] According to Table 2, the practical SI dosage for a long-term study among western females might be around 80–120 mg/day.

Study population

Racial differences. Human studies on the bone protective effects of SI showed a significant race-dependent effect. Compared to Caucasians, Asian females (Japanese, Korean, and Chinese) were more prone to receive beneficial bone-related effects through dietary SI consumption.[18,61,62,73] A U.S. community-based cohort study among 45- to 52-year-old women displayed a positive association of SI intake with BMC for premenopausal Japanese women but no association for Chinese women and perimenopausal Japanese women.[80] In this study, soy intakes of African American and Caucasian women were too low to consider and leave insufficient information for proper analysis. For this result, SI in top-consumed fruits, vegetables, and beverages in the U.S. diet were extremely low[81] may be an explanation.

There may be two causes: (i) most Asian females have habitual lifetime dietary soy intake and (ii) the demographic differences between Asian and Caucasian females. A large prospective cohort study of 24,403 menopausal women in China found that there was an inverse relationship between incidence of bone fracture and soy protein intake ($P < .01$) over the 4.5-year follow-up.[82] In addition, one study also described that SI had better effects in females with estrogen deficiency compared with those with sufficient estrogens.[83] SI effects on bone mass in young menstruating Caucasian women were not as significant as those in Asian women in the same age range. This difference in estrogen status might be the cause of the comparable lower body size among Asian females.[82] Another study further proved that SI intake differed by race and ethnicity was inversely associated with body mass index when total energy intake was adjusted.[84] Similar outcomes might also occur in postmenopausal women.[35,47,59]

Age. A study conducted in Hong Kong suggested that there are different effective dosages of soy intake in females aged 30–40 years compared to 60-year-old females, which indicates that older people might need more soy intake to maintain the lumbar BMD.[85] Studies also presented that SI had a comparable positive protective effect on bone loss among younger postmenopausal women who had last menstruation within 7.5 years.[86] Since there is a rapid bone loss period from 12 to 60 months after the last period, because of the acute loss of estrogen, SI have not shown significant effects in early postmenopausal women with higher estrogen levels. However, Ho *et al.* suggested that a beneficial effect of SI on BMD was less evident in older postmenopausal women compared to younger postmenopausal women.[47]

Moreover, the report by Vupadhyayula *et al.* showed that soy protein isolates containing 90 mg of SI had no effect in an older cohort, with the average age at menopause being 14 years.[76] This might be because of the properties of SI in their inability to reverse the already established bone loss, which was already demonstrated in an animal study, where daily SI intake decreased bone turnover, but did not reverse the established bone loss in adult OVX rats.[87,88]

A 2-year study conducted in Korea showed that there were a few differences in BMD/BMC values among the intake

quartiles in women within the first 4 years of menopause.[89] However, a dose–response relationship, with increasing higher BMD at the trochanter, intertrochanter, and total hip and total body with increasing soy protein intake quartiles ($P < .05$), was found among later postmenopausal women. A prospective cohort study in China also found that soy food consumption was associated with a significantly lower risk of fracture, particularly among women in the early years after menopause.[90] As a result, SI might only perform most effectively within the specific years after menopause while long-term habitual intake has better effects on bone preservation.

Equol and equol producers. Equol is the metabolite of DAN, which has shown to be more potent compared with purified DAN.[91] Equol is not produced in all healthy humans as only 30–60% of the population can produce equol, and production is higher among Asians and vegetarians.[92] Equol and *O*-desmethylangolensin (ODMA) producers were defined as those people with detectable equol (87.5 ng/mL or 362 nM) and ODMA (87.5 ng/mL, or 399 nM) in their urine.[93] Equol possesses more estrogen-like proteins than DAN and plays a crucial role in the soy phytoestrogen efficacy.[91]

Studies showed that compared with GEN, equol had better improved biomechanical and histomorphometric properties in OVX rats; equol (103.8%) and GEN (96.8%) reached similar treatment levels compared with estrogen in the analysis of vertebral body compression strength.[94] Moreover, several studies also demonstrated that long-term equol consumption (10 μg/g bw/day intake for 3 months) provided better bone-sparing effects in OVX rats,[95] while dietary equol (400 mg/kg intake for 6 weeks) decreased weight gain and uterotropic activity.[96] Both estrogen and equol were able to improve fracture healing in OVX-induced osteoporotic bones as reported in the study by Kolios *et al*.[97] According to these studies, it is plausible that equol producers are more responsive to SI than nonproducers because of higher circulating equol concentration in the body.

In contrast, Atkinson *et al.* evaluated the relationship between DAN-metabolizing phenotypes (equol and OMDA) and BMD and body composition in 203 premenopausal women in the United States and found that there were no differences in BMD (hip, spine, femoral neck, and head bone) and body composition between producers and nonproducers in either equol or OMDA producers.[98] These interesting findings might be explained by one other study in premenopausal women, which showed that circulating estrogen and free estradiol concentrations were inversely or not associated with total BMD among equol producers, whereas these hormones were positively associated (*P*-interaction <.05) among equol nonproducers.[98]

In addition, it was also believed that the difference in ability to produce equol between equol producers and nonequol producers is mainly based on the interindividual differences of the intestinal bacteria.[92] A 2-year study also showed that equol-producing intestinal bacteria had no benefit in women who were equol producers. Only women whose 25-hydroxyvitamin D baseline levels were <20 ng/mL had a smaller rate of spinal bone loss in those receiving SI treatment compared with the placebo group.[99] Most likely, since equol producers have positive effects from SI intake, there is a need to have several criteria to be fitted before exerting their most effective protective effects.

Exercise effect on soy isoflavone diets

As commonly known, exercise is a critical factor for the development of healthy skeleton. Weight-bearing exercises, such as walking, running, dancing, and weight training, on a regular basis have a protective effect on bone by improving BMD or decreasing the age-related demineralization of bone. Thus, it might also be important to the protective effects on osteoporotic bone loss.

A 6-week combined intervention study in OVX mice showed that there was a significant protective effect on body fat accumulation in whole body and restoration of bone mass.[100] The effects on the maintenance of bone mass were also found in the study by Shiguemoto *et al.* by combining resistive exercise with soy yoghurt in OVX mice.[101] By applying mechanical vibration treatment with SI diet, the bone quality of OVX rats was significantly improved by increasing bone density and content of sulfated glycosaminoglycan and presenting mature collagen fibers.[102] The clinical application of this combined intervention further proved that the hip BMD of 351 postmenopausal women was well maintained in a study of 2-year exercise training (resistance training 2 d/week and walking 4 d/week) with dietary SI intake (165 mg/day).[103] This study is of clinical importance and may have valued implications for the prevention and treatment of postmenopausal osteoporosis.

In contrast, the moderate-intensity endurance exercise training did not favorably alter bone turnover marker or BMD in a 9-month combination treatment in 61 postmenopausal women.[73] An 8-week study examined the effect of swimming on OVX rats, with soybean protein (0.2 μg/g diet) also showing no effect on both calcium metabolism and bone markers.[104] Exercise might have partial bone site-specific trophic and synergistic effects in addition to the dietary SI, and the conflicting results might be because of the different SI dosages and study durations in these studies, similar as mentioned earlier; while the categories of the exercise training might also make a critical impact on effectiveness of dietary SI.

CONCLUSIONS

In conclusion, the modern applications of SI are based on their estrogenic activities. SI have demonstrated their viable potential in decreasing bone resorption and enhancing formation. Studies using SI to preserve bone loss show more initial promise under *in vitro* and *in vivo* studies. However, further study is warranted to delineate the underlying mechanisms, efficacy, and safety of this compound, and especially, an investigation on the preventive effects of SI on typical human diet and potentials of dietary supplements is critically needed.

In addition, follow-up studies should seek to determine the specific types and location that receive the benefit from SI. Since the bone endpoint selection in literatures was different, it is hard to translate the changes between bone markers and BMD/BMC. Therefore, more well-designed human clinical trials are called for evaluating the effects of

SI on osteoporosis in functional, symptomatic, structural, and biochemical outcomes to build the translation bridge between these endpoints.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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