Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage:www.elsevier.com/locate/apjtm

Document heading doi:

Systematic review of soy isoflavone supplements on osteoporosis in women

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ARTICLE INFO

Article history:
Received 18 November 2011
Received in revised form 15 December 2011
Accepted 15 January 2012
Available online 20 March 2012

Keywords:
Systematic review
Soy isoflavone
Bone mineral density
Urine deoxypyridinoline
Serum bone alkaline phosphatase

ABSTRACT

Objective: To clarify the effect of soy isoflavones on prevention of osteoporosis, and the effective dosage of soy isoflavones and its duration. **Methods:** Random control trials that investigated the association of soy isoflavones and osteoporosis were included in the meta-analysis by researching MEDLINE, EMBASE and the Chinese Biomedical Database up to October 2011. The RevMan software was used for all of the statistical analysis. **Results:** The present meta-analysis found that soy isoflavones significantly increased the bone mineral density by 54% and decreased the bone resorption marker urinary deoxypyridinoline (DPD) by 23% compared to baseline in women. Using random effects model, the effect of isoflavones on bone mineral density (BMD) regarding menopausal status and isoflavone dose revealed higher weighted mean difference changes were found in postmenopausal women and isoflavone dose above 75 mg/d. Subgroup analysis of trials with menopausal status, supplement type, isoflavone dose and intervention duration that used soy isoflavone extracts resulted in significant different overall effect of DPD using by random effects model. Sensitivity analysis indicated that the effect of soy isoflavones on BMD and DPD was robust. **Conclusions:** The present meta-analysis reveals that soy isoflavone supplements significantly increase bone mineral density and decrease the bone resorption marker urinary DPD. It shows no significant effect on bone formation markers serum bone alkaline phosphatase. The significant effect of soy isoflavones on BMD and urinary DPD is relative to menopausal status, supplement type, isoflavone dose and intervention duration.

1. Introduction

The prevalence of age-related bone loss is higher in women than in men, and in 25% to 30% of aging women this loss results in major orthopedic problems[1,2]. Natural or surgical menopause results in an initial phase of rapid bone loss followed by a period of slower deterioration of the skeleton[3,4]. This rapid phase of bone loss occurs within the first 10 years following the cessation of menses or surgical removal of the ovaries. The ovarian hormone deficiency associated with menopause results in increased rate of bone turnover and causes an imbalance between resorption and formation, and thereby accelerates bone loss[5].

Although the optimal treatment of osteoporosis remains controversial, as suggested by Verhaeghe *et al*[5], the most logical approach is to combine an antiresorptive agent to reverse the increased bone remodeling and an agent that stimulates osteblastic proliferation so that bone formation accrues more rapidly. Among the antireorptive agents available today, hormone replacement therapy (HRT) is perhaps the most effective treatment, as it has been shown to both reduce the rate of bone loss[6] and decrease the risk of fracture, including hip fracture[7]. However, not all the patients are willing to initiate this treatment due to a number of undesirable side effects and increased risk of endometrial and breast cancer[8-10] associated with prolonged use of estrogen therapy.

The estrogen-like compounds of plant origin, such as soy isoflavones, have been characterized as naturally occurring selective estrogen receptor modulators with similar beneficial effects to raloxifene on bone[8,11]. The relationships between soybean isoflavones and bone tissue

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have been studied for less than decade. Data from several animal studies have demonstrated that soy isoflavones had bone-conserving effects in the retention of bone mass following ovariectomy[6]. A possible role for soy isoflavones in modifying human bone mass has been suggested by bone *et al*[1]. They found that soy protein supplements enriched in isoflavones attenuated bone loss in postmenopausal and perimenopausal women. Some *in vitro* studies have suggested that isoflavones had biphasic effects, bone formation[1,12] and bone resorption[10]. Epidemiological studies indicate that women who have high soy food consumption have a lower risk of osteoporosis than women who consume a typical Western diet[13-15]. Consequently, many menopausal women use phytoestrogens to maintain their bone mass because they are unlikely to cause the undesirable effects associated with steroid hormones[16]. However, the random control trials on the effect of soy isoflavones on osteoporosis is conflicting, which may be due to the different content of soy isoflavones intake, trail duration and sample size. Therefore, the effects of soy isoflavones on osteoporosis remain unclear. This review of relevant meta-analysis aimed to clarify the effect of soy isoflavones on prevention of osteoporosis, and the effective dosage of soy isoflavones and its duration.

2. Materials and methods

2.1. Study selection

Random control trials that investigated the association of soy isoflavones and osteoporosis were included in the meta-analysis. Trials had to be original data from randomized controlled trials (RCTs) regarding association between soy isoflavones and osteoporosis. Randomizations by clusters or individuals were acceptable. We used no language or publication status restrictions.

2.2. Inclusion and exclusion criteria

Studies were included for systematic review if they met all of the following criteria: 1) included participants of menopausal (peri- or/and postmenopausal) women; 2) evaluated intervention of soy supplements containing isoflavones and clearly described ispflavone dose; 3) contained at least one relevant pair-wise comparison of intervention arms (*i.e.*, soy isoflavone supplements *vs.* placebo, or both plus a non-estrogen add-on), and placebo used did not contain isoflavone or estrogen and was identical or similar in appearance and taste to comparative soy isoflavone supplements; 4) reported outcomes for the effects on at least one of the bone turnover markers. And 5) was a random control trial. Duplicated reports or subgroup analysis of the primary study were excluded.

2.3. Searching strategy for identification of studies

We searched MEDLINE, EMBASE and the Chinese Biomedical Database. The data of the last search was October 2011. We designed a comprehensive and exhaustive search strategy for MEDLINE, EMBASE and the Chinese Biomedical Database databases to identify all relevant studies.

To determine the studies for further assessment, two independent authors reviewed the titles, abstracts and keywords of all records retrieved to determine whether the studies were relevant to this review. Where the title and abstract did not provide adequate information, we assessed the full study and contact the authors of the study if additional information was required for further clarification. Disagreement was resolved by discussion. A total of 679 articles were identified, 32 RCTs regarding soy isoflavones on osteoporosis were included. But 18 studies were excluded due to 16 on the cellular level or animal models and 2 duplicate publications studies. Finally, we yielded 14 RCTs regarding soy isoflavones on osteoporosis. By contracting the related authors of two studies to supplement the missing data, data from one article were obtained, and others were not response or failure to contact. Two independent reviewers independently extract data.

2.4. Statistical analysis

The RevMan software was used for all of the statistical analysis. We would analyze measures using weighted mean difference (WMD) and the 95% confidence interval (*CI*) in the analysis. The heterogeneity was tested with a Q-statistics with P-values < 0.05, and its possible sources were assessed by subgroup analysis as described below. A random-effect model was applied to obtain summary *OR*s and their 95% *CI*. The Egger′s regression asymmetry test was taken to evaluate publication bias (P<0.1 was considered representative of statistically significant publication bias). Subgroup analysis and meta-regressions were performed to investigate possible factors that might relate to varying effects of soy isoflavones on each bone markers across trials, on the basis of menopausal status, supplement type, isoflavone dose and intervention duration. A cut point of 75 mg/day of isoflavone dosage was used, a daily isoflavone intake of up to 75 mg is considered safe by the Japan Food Safety Commission. In addition, meta-regression was used to analyze the association of pre-specified factors with varying effect of isoflavones on different bone turnover markers. a sensitivity analysis was performed to explore robustness of the results.

3. Results

A total of 19 trials were included in this meta-analysis are summarized in Table 1. Data for follow-up durations were

ranged from 1 month to 2 years. In the included studies, participants in the comparison group had similar physical activity patterns and habitual dietary intakes soy isoflavones, calcium, and vitamin D. Most of the studies were designed to maintain the participants' usual diets, lifestyles and body weights. No serious adverse events were reported in the included studies.

Table 2 showed the correlation between BMD and soy isoflavones intake. The random effects model revealed that daily ingestion of soy isoflavones for 1 month to 2 years significantly increased BMD by 54% (95 *CI*: 13% to 94%, *P*<0.001) compared with placebo (Figure 1). Of the 8

Table 1

Characteristics of selected random control trials in the meta-analysis.

Study	Sample (Intervention/ Control)	County	Duration	Participants	Intervention	Control	Outcome
Wong 2009[17]	135/136	USA	2 years	Peri	80 or 120 mg SI /d	Placebo tablets	BMD
Kenny 2009[18]	32/33	USA	1 year	Post	105 mg SI tablets/d	Placebo tablets	BMD
Brink 2008[19]	45/46	France	1 year	Post	90 mg 98.9% pure Ge /d in capsules	Placebo capsules	BAP, DPD
Marini 2007[20]	198/191	Italy	2 years	post	54 mg 98% pure Ge /d	Placebo capsules	BMD,BAP, DPD
Shao 2007[21]	30/30	China	6 months	post	90 mg SI capsule/d	Placebo capsules	BMD,BAP
Wu 2005[22]	34/34	Japan	12 months	post	47 mg SI capsule/d	Placebo capsules	BMD, BAP, DPD
Ye 2006[23]	30/30	China	6 months	post	84 or 126 mg SI capsule/d	Placebo capsules	BMD, DPD
Brooks 2004[24]	13/15	Canada	4 months	post	41.9 mg Ge flour/d	Placebo capsules	DPD, BAP
Harkness 2004[25]	19/19	USA	1 year	post	110 mg SI capsules/d	Placebo capsules	BMD
Kreijkamp-kaspers 2004[26]	88/87	Netherlands	1 year	post	99 mg SI capsules/d	Placebo capsules	BAP
Nikander 2004[27]	28/28	Finland	6 months	post	114 SI capsules/d	Placebo capsules	DPD
Dalais 2003[28]	38/40	Australia	3 months	post	69 mg SI capsules/d	Placebo capsules	DPD
Uesugi 2002[29]	12/11	Japan	1 month	Peri	38.4 mg SI capsules/d	Placebo capsules	DPD
Yamori 2002[30]	20/20	Brazil	2.5 months	post	22.7 mg SI scapsules/d	Placebo capsules	DPD

Ge: genistein; SI: soy isoflavones; BMD: bone mineral density (mg/cm^2); DPD: urine deoxypyridinoline (nmol/mmol creatinine, unless specified); BAP: serum bone alkaline phosphatase (U/L, unless specified).

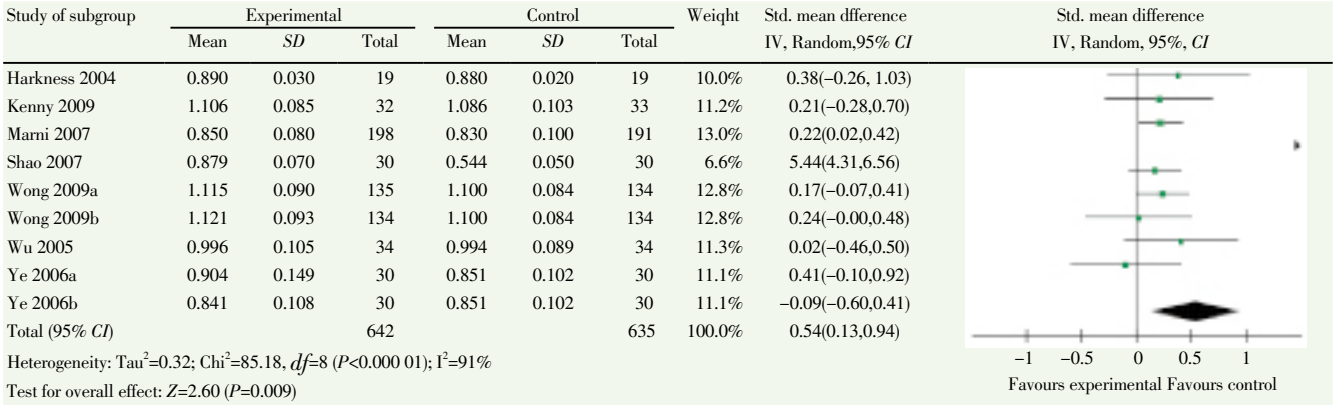

Figure 1. Effects of soy isoflavones on BMD (%).

Mean difference, mean percentage changes (%) of BMD from baseline for soy isoflavones minus that for placebo.

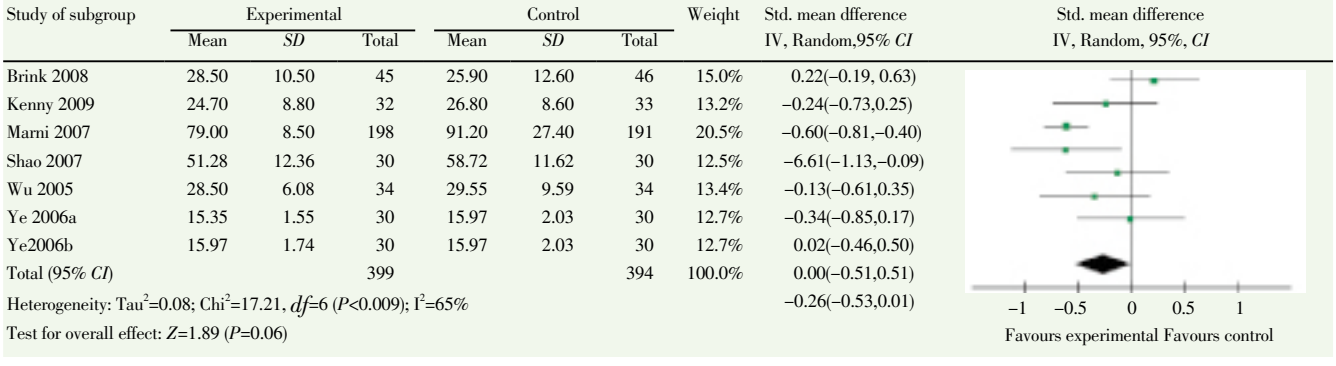

Figure 2. Effects of soy isoflavones on serum BAP (%).

Mean difference, mean percentage changes (%) of urine BAD from baseline for soy isoflavones minus that for placebo.

included trials, 8 trials resulted in positive mean difference in percentage change from baseline between isoflavone and placebo arms. The combined percentage change of urine BAD from baseline for soy isoflavones and placebo were decreased by 26% (53% to −1%). Additionally, for urine DPD, soy isoflavones decreased DPD from baseline by 23% (2% to 44%).

Results of subgroup analysis of the effects of isoflavones on BMD and DPD based on the four pre-specified factors (menopausal status, supplement type, isoflavone dose, and intervention duration) are showed in Table 2 and Table 3. Using random effects model, the effect of isoflavones on BMD regarding menopausal status and isoflavone dose revealed higher WMD changes were found in postmenopausal women and isoflavone dose above 75 mg/d. Subgroup analysis of trials with menopausal status, supplement type, isoflavone dose and intervention duration that used soy isoflavone extracts resulted in significant different overall effect of DPD using by random effects model. The meta regression analysis did not show the menopause status, supplement type, isoflavone dose and intervention duration were significantly associated with the varying effects of isoflavones on BMD and DPD across included trails.

The funnel plots did not indicated obvious publication bias. The sensitivity analysis did not result in significantly different overall effect of soy isoflavones on BMD, BAP and DPD after excluding trails with small sample, <6 months intervention duration and isoflavone dose ⩽75 mg/d.

4. Discussion

The present meta-analysis found that soy isoflavones significantly increased the bone mineral density by 54% and decreased the bone resorption marker urinary DPD by 23% compared to baseline in women. Sensitivity analysis

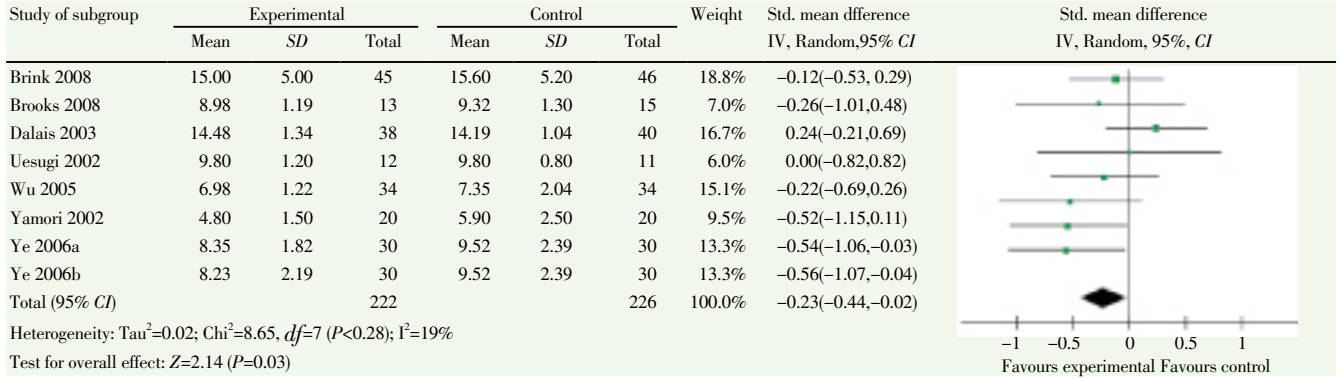

Figure 3. Effects of soy isoflavones on urine DPD (%).
Mean difference, mean percentage changes (%) of urine DPD from baseline for soy isoflavones minus that for placebo.

Table 2
Subgroup analysis of the effects of soy isoflavones on BMD (%)

Variables		Trials	Sample size	P value for heterogeneity	Fixed effect model	
					WMD	95% *CI* (%)
Menopausal status	Perimenopausal	1	269/268	–	0.20	0.03, 0.37
	Postmenopausal	6	423/416	0.001	0.77	0.1, 1.43
Isoflavone dose	⩽75 mg/d	1	34/34	–	0.19	0.01, 0.37
	>75 mg/d	6	658/650	<0.001	0.75	0.16, 1.34

Table 3
Subgroup analysis of the effects of soy isoflavones on urine DPD (%).

Variables		Trials	Sample size	*P* value for heterogeneity	Fixed effect model	
					WMD	95% *CI* (%)
Menopausal status	Perimenopausal	1	34/34	–	0.00	−0.82, 0.82
	Postmenopausal	7	216/220	0.21	−0.25	−0.48, −0.02
Supplement type	Isoflavone extracts	5	250/254	0.11	−0.30	−0.53, −0.07
	Soy foods with isoflavones	3	179/179	0.61	−0.13	−0.62, 0.36
Isoflavone dose	⩽75 mg/d	3	133/134	0.30	−0.37	−0.67, −0.07
	>75 mg/d	5	117/120	0.35	−0.11	−0.38, 0.17
Intervention duration	⩽6 months	5	250/254	0.53	−0.30	−0.53, −0.07
	>6 months	3	179/179	0.13	−0.13	−0.62, 0.36

indicated that the effect of soy isoflavones on BMD and DPD was robust. The postmenopausal women experience a sharp decrease in estrogen concentration that could lead to an increase rate of bone remodeling, and the increase bone remodeling is associated with both decreased BMD and increased risk of fracture[1,31,32]. Therefore, our meta-analysis showed that soy isoflavone supplements might be associated to increased BMD and decrease risk of fracture in menopausal women.

Our meta-analysis showed the BMD could be increased by 54% in women with supplement isoflavones. The mechanism mediating the improvement of BMD by soy isoflavones is not well understood, but it may be a result of their chemical and biological similarity to mammalian estrogens, which are known to increase BMD in menopausal women[1,31]. Previous study showed the magnitude of significant effect of soy isoflavone extracts in increasing lumbar spine BMD by 20.3 mg/cm^2, and Ma *et al*[33] described in their meta-analysis a subgroup of several RCT testing isolated soy protein resulted in a significant increase in spine BMD by 21.3 (95% *CI*: 3-39.7 mg/cm^2). This result is consistent with ours, which indicated that soy isoflavones ingested either alone in extracted form or as constituent parts of isolated soy protein beneficially increase BMD in women.

The The directions of the overall effect of soy isoflavone supplements on urine DPD and results of subgroup analyses on the basis of menopausal status were consistent with those demonstrated in a previous meta-analysis[33]. These indicated that soy isoflavone supplements, especially when ingested in extract form and when ingested by postmenopausal women, exert significant effects in decreasing the bone resorption marker DPD. Our meta-analysis has more completely and more precisely clarified the effect of soy isoflavones on DPD by including additional studies and limiting the combining outcomes of percentage change from baseline. We observed differences in effects on DPD between subgroups on bases of menopause status supplement type, isoflavone dose and intervention duration, which can be explained the limited numbers of RCTs in each subgroup could limit the statistic power. Further studies are needed to clarify the particular subgroups, duration, dose and menopause status and intervention duration that may increase or decrease the magnitude of the effects of soy isoflavone supplements on DPD.

There were several limitations of this meta-analysis. Firstly, there is existence of the significant heterogeneity in the effects of soy isoflavone supplement on BMD, urine DPD and serum BAP.

on urine DPD, and some heterogeneity still existed after performing the subgroup analysis, suggesting that other factors should have been taken into account in the analysis. The heterogeneity of results across trials, which could be explained, might also be induced by differences in habitual, dietary intake of soy isoflavones, chemical forms and proportions of individual soy isoflavones. Another limitation was that meta-regressions analyzing each pre-specified factors did not reveal these factors to be associated with the various effects across trials, which could be explained the limited number of studies.

In conclusion, the present meta-analysis revealed that soy isoflavone supplements significantly increased bone mineral density and decreased the bone resorption marker urinary DPD and showed no significant effect on bone formation markers serum BAP. The significant effect of soy isoflavones on BMD and urinary DPD was modified by menopausal status, supplement type, isoflavone dose and intervention duration. These findings may provide more information to the prevention of osteoporosis. Further studies also need to address factors relating to verify the effects of soy isoflavones on the bone turnover markers.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] Bone HG, Greenspan SL, McKeever C. Alendronate and estrogen effects in postmenopausal women with low bone mineral density alendronate/estrogen study group. *J Clin Endocrinol Metab* 2000; **85**(2): 720-726.

[2] Garn SM. Bone loss and aging. In: Goldman R RM. *Physiological and pathology of human aging*. New York: Academic Press Inc; 1975.

[3] Gallagher JC. The pathogenesis of osteoporosis. *Bone Miner* 1990; **9**: 215-227.

[4] Stepan JJ, Pospichal J, Presl J, Pacovsky V. Bone loss and biochemical indices of bone remodeling in surgically induced postmenopausal women. *Bone* 1987; **8**: 279-284.

[5] Verhaeghe J, Van Bree R, Van Herck E, Thomas H, Skottner A, Dequeker J, et al. Effects of recombinant human growth hormone and insulin-like growth factor-I, with and without 17-estradiol, on bone and mineral homeostasis of aged ovariectomized rats. *J Bone Miner Res* 1996; **11**: 1723-1735.

[6] Genant HK, Baylink DJ, Gallagher JC. Estrogens in the prevention of osteoporosis in postmenopausal women. *Am J Obstet Gynecol* 1989; **161**: 1842-1846.

[7] World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis, Report of the WHO Study Group World Health Organ Tech Rep Ser. *World Health Organization* 1994; **843**: 1-129.

[8] Henderson BE, Ross RK, Pike MC. Hormonal chemoprevention of cancer in women. *Science* 1993; **259**: 633-638.

[9] Judd HL, Meldrum DR, Deftos LJ, Henderson BE. Estrogen replacement therapy: indications and complications. *Ann Int Med* 1983; **98**: 30-37.

[10] Collaborative Group on Hormonal Factors in Breast Cancer. Collaborative group on hormonal factors in breast cancer. *Lancet*

1997; **350**: 1047-1059.

[11]Brezinski A, Debi A. Phytoestrogens: the "natural" selective estrogen receptor modulators. *Eur J Obstet & Gynecol & Rep Bio* 1999; **85**: 47-51.

[12]Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. The use of biochemical markers of bone turnover in osteoporosis Committee of Scientific Advisors of the International Osteoporosis Foundation. *Osteoporos Int* 2000; **11**(Suppl): S2-17.

[13]Adlercreutz H, Mazur W. Phyto-oestrogens and Western diseases. *Ann Med* 1997; **29**:95-120.

[14]Somekawa Y, Chiguchi M, Ishibashi T, Aso T. Soy intake related to menopausal symptoms, serum lipids, and bone mineral density in postmenopausal Japanese women. *Obstet Gynecol* 2001; **97**(1): 109-115.

[15]Zhang X, Shu XO, Li H, Yang G, Li Q, Gao YT, et al. Prospective cohort study of soy food consumption and risk of bone fracture among postmenopausal women. *Arch Intern Med* 2005; **165**(16): 1890-1895.

[16]Messina MJ. Soy foods and soybean isoflavones and menopausal health. *Nutr Clin Care* 2002; **5**(6): 272-282.

[17]Wong WW, Lewis RD, Steinberg FM, Murray MJ, Cramer MA, Amato P, et al. Soy isoflavone supplementation and bone mineral density in menopausal women: a 2-y multicenter clinical trial. *Am J Clin Nutr* 2009; **90**: 234-242.

[18]Kenny AM, Mangano KM, Abourizk RH, Bruno RS, Anamani DE, Kleppinger A. Soy proteins and isoflavones affect bone mineral density in older women: a randomized controlled trial. *Am J Clin Nutr* 2009; **90**: 234-242.

[19]Brink E, Coxam V, Robins S, Wahala K, Cassidy A, Branca F. Long-term consumption of isoflavone-enriched foods does not affect bone mineral density, bone metabolism, or hormonal status in early postmenopausal women: a randomized, double-blind, placebo controlled study. *Am J Clin Nutr* 2008; **87**: 761-770.

[20]Marini H, Bitto A, Altavilla D, Burnett BP, Polito F, Di Stefano V. Breast safety and efficacy of genistein aglycone for postmenopausal bone loss: a follow-up study. *J Clin Endocrinol Metab* 2008; **93:** 4787-4796.

[21]Shao XJ, Ye ZQ, Luo CX, Cai DZ. Effect of soy isoflavones on osteoporosis in postmenopausal women. *Academic J Sun Yat-Sen Univ* 2007; **28:** 241-242.

[22]Wu CF, Wu DC, Hsu HK, Kao EL, Lee JM, Lin CC, et al. Relationship between genetic polymorphisms of alcohol and aldehyde dehydrogenases and esophageal squamous cell carcinoma risk in males. *World J Gastroenterol* 2005; **11**: 5103-5108.

[23]Ye YB, Tang XY, Verbruggen MA, Su YX. Soy isoflavones attenuate bone loss in early postmenopausal Chinese women: a single-blind randomized, placebocontrolled trial. *Eur J Nutr* 2006; **45**: 327-334.

[24]Brooks JD, Ward WE, Lewis JE, Hilditch J, Nickell L, Wong E. Supplementation with flaxseed alters estrogen metabolism in postmenopausal women to a greater extent than does supplementation with an equal amount of soy. *Am J Clin Nutr* 2004; **79**: 318-325.

[25]Harkness LS, Fiedler K, Sehgal AR, Oravec D, Lerner E. Decreased bone resorption with soy isoflavone supplementation in postmenopausal women. *J Womens Health* (Larchmt) 2004; **13**: 1000-1007.

[26]Kreijkamp-Kaspers S, Kok L, Grobbee DE, de Haan EH, Aleman A, Lampe JW. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. *JAMA* 2004; **292**: 65-74.

[27]Nikander E, Metsä-Heikkilä M, Ylikorkala O, Tiitinen A. Effects of phytoestrogens on bone turnover in postmenopausal women with a history of breast cancer. *J Clin Endocrinol Metab* 2004; **89**(3): 1207-1212.

[28]Dalais FS, Ebeling PR, Kotsopoulos D, McGrath BP, Teede HJ. The effects of soy protein containing isoflavones on lipids and indices of bone resorption in postmenopausal women. *Clin Endocrinol* (*Oxf*) 2003; **58**: 704-709.

[29]Uesugi S, Watanabe S, Ishiwata N, Uehara M, Ouchi K. Effects of isoflavone supplements on bone metabolic markers and climacteric symptoms in Japanese women. *Biofactors* 2002; **22**: 221-228.

[30]Yamori Y, Moriguchi EH, Teramoto T, Miura A, Fukui Y, Honda KI. Soybean isoflavones reduce postmenopausal bone resorption in female Japanese immigrants in Brazil: a ten-week study. *J Am Coll Nutr* 2002; **21**: 560-563.

[31]Nielsen TF, Ravn P, Bagger YZ, Warming L, Christiansen C. Used estrogen therapy in prevention of postmenopausal osteoporosis. A 2-year randomized, double blind, placebo-controlled study. *Osteoporos Int* 2004; **15**: 168-174.

[32]Seeman E. Estrogen, androgen, and the pathogenesis of bone fragility in women and men. *Curr Osteoporos Rep* 2004; **2**: 90-96.

[33]Ma DF, Qin LQ, Wang PY, Katoh R. Soy isoflavone intake increases bone mineral density in the spine of menopausal women: meta-analysis of randomized controlled trials. *Clin Nutr* 2008; **27**(1): 57-64.