Isoflavone combined with exercise on bone mineral density in postmenopausal women: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: This meta-analysis of randomized control trials (RCTs) aimed to evaluate the effects of isoflavones supplementation combined with exercise training on bone mineral density (BMD) in postmenopausal women.

Methods: Two reviewers did a complete search of two electronic database (Medline, PubMed) records up to January 31, 2019. Risk of bias was classified based on the Cochrane Collaboration tool. The pooled standard mean difference (SMD) combined with 95% confidence interval (CI) was used as the effect size of BMD values.

Results: A total of four RCTs with 609 participants were included for meta-analysis. The BMD did not differ significantly between isoflavone supplementation combined with exercise training group and placebo group (sub-whole body: SMD = 0.00, 95% CI, –0.23 to 0.24; lumbar spine: SMD = 0.15, 95% CI, –0.30 to 0.60; total hip: SMD = 0.05, 95% CI, –0.18 to 0.298; femoral neck: SMD = 0.10, 95% CI, –0.23 to 0.43; trochanter: SMD = 0.09, 95% CI, –0.14 to 0.33; ward's triangle: SMD = –0.03, 95% CI, –0.24 to 0.30). In addition, combined intervention did not provide additive effects on BMD improvements compared with exercise or isoflavone supplementation alone. The trials included in this meta-analysis were small and some had methodological limitations.

Conclusion: The present meta-analysis reveals that isoflavone supplements combined with exercise training do not significantly increase BMD in postmenopausal women. In addition, combined intervention does not provide additive effects on BMD improvements compared with exercise or isoflavone supplementation alone.

Keywords: Bone density; Isoflavones; Postmenopause

1. INTRODUCTION

Menopause, characterized by a decreased level of estrogen, is often related to the morbidity and mortality of several chronic diseases, such as osteoporosis, cardiovascular disease, and obesity.[1] Osteoporosis is reported to be linked to an increased risk of osteoporotic fracture, which would lead to higher healthcare costs, disability, and excess mortality.[2] Low bone mineral density (BMD) has been considered to be a hallmark of osteoporosis, as well as a predictor of osteoporotic fracture.[3] It is indicated that hormone replacement therapy (HRT) can prevent osteoporotic fracture, although it suffered from greater risks, such as breast cancer, than benefits, such as reduced fractures.[4] US Preventive Services Task Force (USPSTF) recommends that postmenopausal women may not use both estrogen and progestin for the primary prevention of chronic diseases.[5] Many women have therefore turned to alternative therapies, including exercise and eating some specific foods.

Many reports have suggested that although the effects are small, exercise has a beneficial effect on bone health in postmenopausal women, with BMD of the proximal femur or lumbar spine increasing 1% to 2% per year.[6] Additionally, soy foods contain isoflavones, which are structurally similar to 17-beta-estradiol and can act as estrogen antagonists in some cases and estrogen agonists in others.[7] Results from researches of estrogen-deficient animals and postmenopausal women have suggested that soy foods are not as steroid hormones to result in undesirable side effects,[8] they have therefore received a lot of attention for their preventive role in osteoporosis.[9] Recently, prospective epidemiologic studies from both Asian and United States[10–12] have shown that soy foods intake is associated with a significantly lower risk of fracture or developing osteoporosis.

To date, several systematic review and meta-analyses[9,13–16] have been performed to examine the effects of either isoflavone supplementation or exercise on BMD. Then, whether there is a potential synergistic action of isoflavone supplementation with exercise on bone health in postmenopausal women? Several randomized controlled trials (RCTs) have been conducted to examine the effects of the combined treatment on BMD in

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postmenopausal women.[17–21] Therefore, to obtain a more accurate and precise estimated effect of the combined treatment against decreased BMD, we conducted a comprehensive meta-analysis of RCT studies. This meta-analysis followed the guideline on meta-analysis of observational studies in epidemiology (MOOSE).[22]

2. METHODS

2.1. Literature search

Two investigators (Q.S.M. and M.Y.) independently screened the original articles published in English language through PubMed (database root [1964] to January 31, 2019) and EMBASE (database root [1974] to January 31, 2019). The relevant studies were searched with the following text word and/or Medical Subject Heading (MeSH) terms: (1) exercise OR physical activity OR walking OR motor activity; (2) soy OR tofu OR miso OR natto OR soybeans OR soymilk OR genistein OR daidzein OR isoflavones OR phytoestrogens; and (3) randomized or trials or controlled. Moreover, the reference lists of the included articles and published reviews were also screened and hand-searched. When two or more papers contained the same or some of the same study population, the paper that described the largest population was used.

2.2. Inclusion and exclusion criteria

Two reviewers (Q.S.M. and M.Y.) independently reviewed all the retrieved studies to determine if they meet the inclusion criteria. A third independent reviewer (JCM) was consulted when reviewers' evaluations were not in consensus. Articles would be included in this meta-analysis if they met the following inclusion criteria:

- Being a randomized controlled trial design;
- The participants in the studies were postmenopausal women;
- Being healthy and without cancer or other severe acute and chronic diseases (e.g., diabetes, hypertension, heart diseases, and neurological diseases);
- With the use of dual-energy X-ray absorptiometry (DXA) as a measurement marker for BMD;
- Reported mean change in BMD from baseline to the end of the study along with corresponding SDs, SEMs, or 95% confidence intervals (CIs);

The exclusion criteria were as follows:

- The results of BMD measurement were unavailable for statistical analysis.
- Only abstracts were available, and incomplete data were reported.
- Participants had used hormone therapy or selective estrogen receptor modulator preparations during or ≤3 months before initiation of the trial.

2.3. Data extraction

After the completion of article screening, two investigators (Q.S.M. and M.Y.) independently extracted the data from the eligible studies according to the predesigned protocol. The extracted information was as follows: the first author's name, publication year, geographical area of study population, age and gender of the participants, sample size of the intervention and control groups, intervention frequency, and duration. Differences in data extraction between investigators were resolved by consensus.

2.4. Assessing the risk of bias

The quality of the included articles was assessed objectively and comprehensively by two reviewers (S.-m.Q. and Y.M.). Disagreements regarding the appraisal of methodological quality were resolved through discussion between the reviewers. If an agreement could not be reached, a third reviewer made the final decision. To assess the quality of RCTs, "The Cochrane Collaboration's tool" was used, which comprises selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome data), attribution bias (incomplete outcome data), reporting bias (selective reporting), and other sources of bias. The Cochrane risk of bias in individual studies was judged to be at a "low," "high," or "unclear".[23]

2.5. Data analysis and synthesis

The targeted RCTs compared a combination of isoflavone supplementation and exercise training with controls receiving either placebo or isoflavone supplementation only or exercise only. All statistical analyses were performed using STATA, version 11.0 (STATA, College Station, TX, USA) statistical software. A two-tailed p value of <0.05 represents significance. Standardized mean differences (SMDs) and 95% CIs were calculated via the pooled effect size of continuous data in order to estimate BMD values in the intervention and control groups. In light of the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. This method of a random-effects model was developed by DerSimonian and Laird.[24]

Heterogeneity was assessed using the Cochran Q and I^2 statistics. For the Q statistic, a p value of <0.10 was considered statistically significant for heterogeneity; for the I^2 statistic, which explain the amount of total variation among studies, heterogeneity was interpreted as absent (I^2 = 0%–25%), low (I^2 = 25.1%–50%), moderate (I^2 = 50.1%–75%), or high (I^2 = 75.1%–100%).[25] To assess the influence of each individual study to the overall estimates of the rest of the studies, leave-one-out sensitivity analysis was performed by removing one study at a time to confirm that the findings were not influenced by any single study.

3. RESULTS

3.1. Study selection process

Figure 1 shows the flowchart for the selection of the studies for this systematic review and meta-analysis. Using this approach, we identified a total of 1398 publications (256 from PubMed, 1140 from EMBASE). After the exclusion of duplicates and reviewing the title and abstract of the retrieved publications, 36 publications were found. Hand-searching of the bibliographies did not produced additional articles. Therefore, a total of 36 references were retrieved for full-text screening. After excluding studies that did not meet the inclusion criteria, a total of four articles[17–20] were included in the systematic review and meta-analysis. The most common reasons for exclusion were a lack of data on intake of soy isoflavones and/or exercise on the BMD (n = 29 studies). One article[19] was only included as systematic review because it reported the relative changes in BMD between a combination of isoflavone supplementation and exercise training and placebo groups. Therefore, a total of three articles[17,18,20] were included in the meta-analysis (Fig. 1).

3.2. Characteristics of eligible articles

The relevant data from the selected articles are summarized in Table 1. The four articles were published between 2006 and 2013, and two studies[17,19] were conducted in the United States,

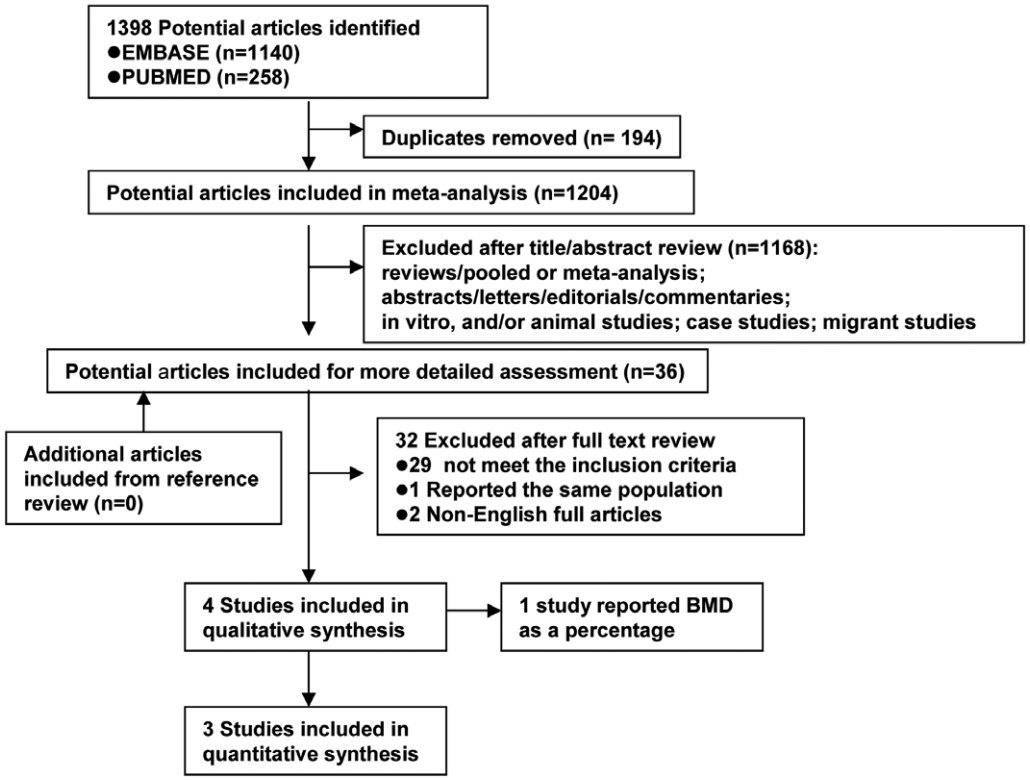

Fig. 1 The flowchart for the selection of the studies for this systematic review and meta-analysis. BMD = bone mineral density.

Table 1

Characteristics of included articles

First author name/ year/country	Participants	Duration	Isoflavone intervention	Exercise intervention	Outcome
Wu/2006/Japan[20]	N = 136; age: 45–60 years No HRT, lipid-lowering medications, antibiotics, or any other medication known to affect the skeleton	12 mo	T: Isoflavone, 75 mg/d C: Placebo capsules, 2/d	T: Walking, 60 min, 3 d/wk C: Maintain usual activities	BMD
Evans/2007/USA[19]	N = 43; age: 50-65 years No HRT, not taking medications known to alter bone metabolism	9 mo	T: Isoflavone, 91.2 mg/d C: Milk protein isolate	T: Moderate endurance exercise, 3 d/wk C: Maintain usual activities	BMD
Choquette/2011/ Canada[18]	N = 79; age: 50-70 years Overweight or obese No HRT; no medication that influences glucose or lipid metabolism	6 mo	T: Isoflavone, 70 mg/d C: Placebo capsules, 2/d	T: 30 min of resistance training + 30 min of aerobic exercise, 3 d/wk C: Maintain usual activities	BMD
Chilibeck/2013/USA[17]	N = 351; age: 55.8 ± 5.0 years No HRT, not taking medications known to alter bone metabolism	2 yr	T: Isoflavone, 165 mg/d C: Placebo	T: Strength training + brisk walking, 2 d/wk C: A home-based flexibility program, 2 d/wk	BMD

BMD = bone mineral density; C= control; HRT = hormone replacement therapy; T = treatment.

and one in Canada[18] and Japan,[20] respectively. Healthy postmenopausal women were recruited in all but one study,[18] which recruited overweight or obese women. All these participants did not take medications known to alter bone metabolism. The sample sizes ranged from 43[19] to 351,[17] with a total of 609 participants were included for analysis. The exercise interventions included aerobic exercise, resistance training, strength training, walking, and endurance exercise. The isoflavone interventions included 70, 75, 91.2, and 165 mg of isoflavone conjugate, respectively. The durations of experimental intervention were 6, 9, 12 and 24 months, respectively. In three studies,[17,18,20] the control groups received usual activities and took placebo, and in the remaining one study,[19] the control groups received usual activities and took milk protein isolate.

3.3. Risk of bias

The Cochrane risk of bias assessment of the included articles is illustrated in Table. 2. All studies used clear inclusion/exclusion criteria, but only one study[18] described withdrawal and dropouts. All of the included studies utilized randomization, provided details of isoflavone supplementation combined with exercise training intervention and appropriate data analysis.

Table 2

Risk of bias summary for each study

Author name/year of publication	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of assessment	Missing data	Selective reporting	Other
Wu/2006[20]	?	0	0	?	1	1	?
Choquette/2011[18]	?	0	0	?	1	1	?
Chilibeck/2013[17]	1	0	0	1	1	1	?
Evans/2007[19]	1	0	0	1	1	1	?

1 = design and methodology feature adequately reported; 0 = design and methodology feature not adequately reported; ? = design and methodology feature unclearly reported.

However, only two studies[17,19] provided the randomization process, and no studies gained point for blinding, because blinding was only used for pharmacological interventions. The quality score of the included studies was relatively low.

3.4. Isoflavone supplementation combined with exercise training versus placebo

Figure 2 shows the results of meta-analysis for isoflavone supplementation combined with exercise training versus placebo. Three studies[17,18,20] reported results for BMD in sub-whole body, lumbar spine, hip regions, femoral neck, and trochanter, respectively, and two RCTs[17,18] for BMD in ward's triangle. Overall, there was no any significant heterogeneity for BMD change in all but one regions (lumbar spine, p = 0.063). The BMD in all these regions did not differ significantly between isoflavone supplementation combined with exercise training group and placebo group (sub-whole body: SMD = 0.00, 95% CI, –0.23 to 0.24; lumbar spine: SMD = 0.15, 95% CI, –0.30 to 0.60; total hip: SMD = 0.05, 95% CI, –0.18 to 0.29; femoral neck: SMD = 0.10, 95% CI, –0.23 to 0.43; trochanter: SMD = 0.09, 95% CI, –0.14 to 0.33; and ward's triangle: SMD = –0.03, 95% CI, –0.24 to 0.30).

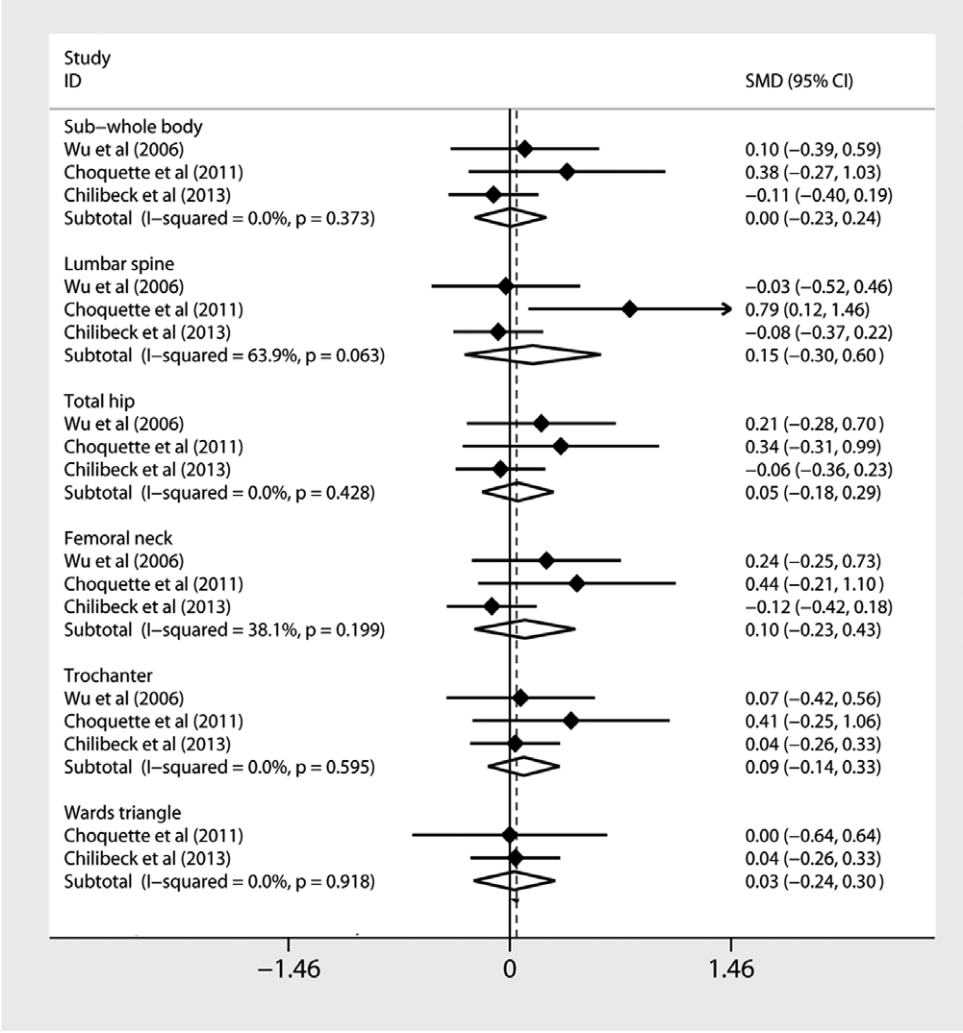

Fig. 2 Forest plot showing the difference in bone mineral density change in sub-whole body, lumbar spine, total hip, femoral neck, trochanter, and ward's triangle for isoflavone supplementation combined with exercise training along with placebo. CI = confidence interval; SMD = standard mean difference.

3.5. Isoflavone supplementation combined with exercise training versus isoflavone supplementation alone

Results from Evans et al[19] showed that at 9 months, there was no significant effects of soy protein isolate combined with moderate exercise versus soy alone on BMD in the total body, lumbar spine, and proximal femur in postmenopausal women. As shown in Fig. 3, three RCTs reported results for BMD in sub-whole body, lumbar spine, hip regions, femoral neck, trochanter, respectively, and two RCTs for BMD in ward's triangle for isoflavone supplementation combined with exercise training versus isoflavone supplementation alone. In total, results for BMD did not exhibit any significant heterogeneity and did not differ significantly (sub-whole body: SMD = 0.14, 95% CI, –0.10 to 0.37, p = 0.643; lumbar spine: SMD = 0.15, 95% CI, –0.16 to 0.46, p = 0.239; total hip: SMD = 0.08, 95% CI, –0.22 to 0.37, p = 0.258; femoral neck: SMD = 0.11, 95% CI, –0.26 to 0.49, p = 0.136; trochanter: SMD = 0.12, 95% CI, –0.12 to 0.35, p = 0.539; ward's triangle: SMD = –0.02, 95% CI, –0.03 to 0.17, p = 0.938).

3.6. Isoflavone supplementation combined with exercise training versus exercise training alone

Results from Evans et al[19] showed that at 9 months, there was no additive effects of soy combined with moderate exercise versus exercise and milk protein isolate on BMD in the total body, lumbar spine, and proximal femur in postmenopausal women. As shown in Fig. 4, change in BMD in all these regions did not differ significantly for isoflavone supplementation combined with exercise training versus exercise training alone (sub-whole body: SMD = 0.09, 95% CI, –0.15 to 0.33; total hip: SMD = 0.22, 95% CI, –0.32 to 0.7; lumbar spine: SMD = 0.12, 95% CI, –0.12 to 0.36; femoral neck: SMD = 0.20, 95% CI, –0.25 to 0.66; trochanter: SMD = 0.21, 95% CI, –0.18 to 0.59; ward's triangle: SMD = 0.46, 95% CI, –0.48 to 1.40). There was no any significant heterogeneity for BMD change in all but three regions (total hip: p = 0.025; femoral neck: p = 0.070; ward's triangle: p = 0.014).

3.7. Adverse events related to interventions

Two studies[17,18] reported adverse events possibly related to interventions. Results from Chilibeck et al[17] showed that out of 351 women randomized, there were 5 serious adverse events, 6 adverse events detected with mammography and 4 with respect to changes endometrial thickness (Supplementary Table 1, http://links.lww.com/JCMA/A54). **The researchers also reported that t**he groups taking isoflavone had significantly lower (24/177; 14%) adverse events related to menopausal symptoms compared with the groups not taking

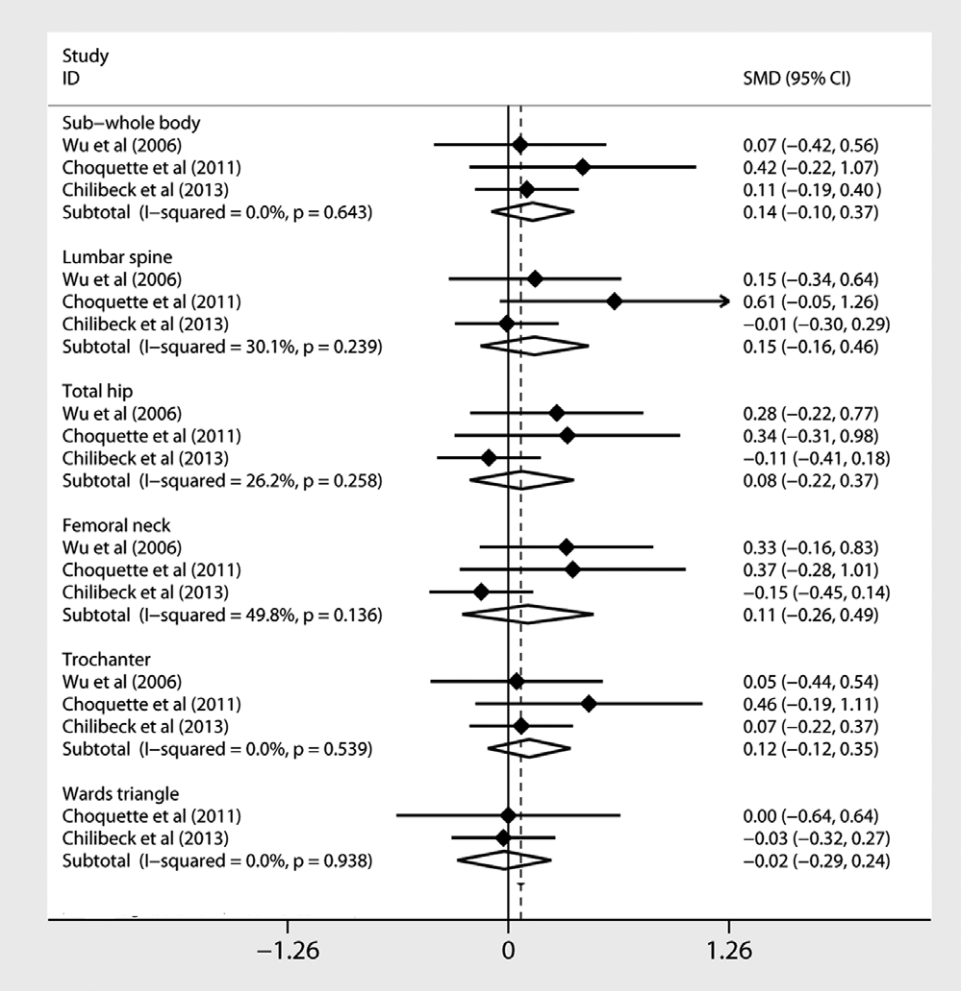

Fig. 3 Forest plot showing the difference in bone mineral density change in sub-whole body, lumbar spine, total hip, femoral neck, trochanter, and ward's triangle for isoflavone supplementation combined with exercise training along with isoflavone supplementation alone. CI = confidence interval; SMD = standard mean difference.

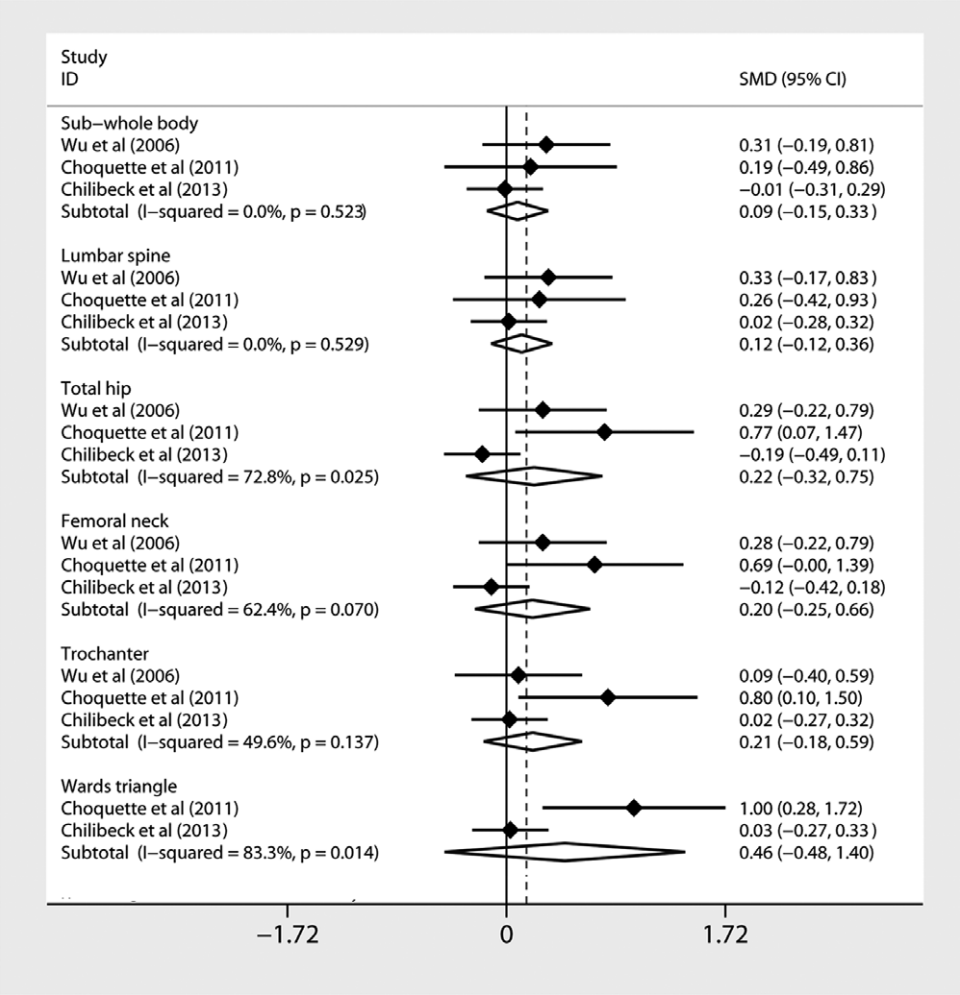

Fig. 4 Forest plot showing the difference in bone mineral density change in sub-whole body, lumbar spine, total hip, femoral neck, trochanter, and ward's triangle for isoflavone supplementation combined with exercise training along with exercise training alone. CI = confidence interval; SMD = standard mean difference.

isoflavone (58/174; 33%; $p < 0.01$). Results from Choquette et al[18] showed that many women in the exercise groups reported an increase in hot flashes.

3.8. Publication bias and sensitivity analysis

Because the number of included articles was small, publication bias analysis was not conducted. We also conducted a sensitivity analysis by omitting one study at a time and calculating the SMD change for the remainder of studies and found that there were no changes in the direction of effect when any one study was excluded. This is true when isoflavone supplementation combined with exercise training versus placebo group (Supplementary Table 2, http://links.lww.com/JCMA/A54), isoflavone supplementation alone group (Supplementary Table 3, http://links.lww.com/JCMA/A54), and exercise alone group (Supplementary Table 4, http://links.lww.com/JCMA/A54), respectively.

4. DISCUSSION

The present study examined the combined effects of exercise and isoflavone supplementation on BMD in postmenopausal women. Compared with controls who received placebo and/or maintained usual activity, exercise combined with isoflavone supplementation intervention did not show improvements in BMD in sub-whole body, lumbar spine, hip regions, femoral neck, trochanter, and ward's triangle, respectively. In addition, the combined intervention did not provide additive effects on BMD improvements compared with either one intervention alone.

Results from Choquette et al[18] showed that no changes could be observed in BMD after 6 months of resistance training and aerobic exercise plus isoflavone supplementation, which was also the case after 4 months of aerobic training in the study of Evans et al[19] In comparison, Wu et al[20] observed mainly a preventive effect on the loss in BMD at the hip after a 12-month period, for walking exercise combined with isoflavones. Even, study from Chilibeck et al[17] observed that combined treatments resulted in decreased BMD at total hip, narrow neck, and femoral shaft along with the control group.

Several meta-analyses[9,26–28] of RCTs have evaluated the effects of soy isoflavones on BMD and have suggested a preventive role in BMD loss, A recent meta-analysis,[9] which included 26 RCTs (n = 2652), found that isoflavone treatment was associated with a significantly higher weighted mean difference (WMD) of BMD change at lumbar spine and femoral neck than the control. The mechanism mediating the improvement of BMD by soy isoflavones is not well understood, but it may be related to their chemical and biological similarity to estrogens. Isoflavones may combine the estrogen receptor (ER)-α and ER-β expression and

stimulate estrogen activity, thus affecting elements' content in bones.[29,30] Early smaller, less well-controlled studies in humans showed that soy isoflavones can significantly increase bone formation and decrease bone resorption.[31] Actually, recently published RCTs with relatively large sample sizes (n > 200) found no effect of soy isoflavones on lumbar spine or hip BMD.[32,33] Results from Levis et al[33] showed that in postmenopausal women aged 45 to 60 years, no significant differences were found between the participants receiving 200 mg/day of soy isoflavones (n = 122) and those receiving placebo (n = 126) regarding BMD changes in the spine, the total hip, or the femoral neck. Additionally, the summary analysis[34] suggested that resistance exercise interventions were effective in preserving BMD at the femoral neck and lumbar spine in postmenopausal women.

As denoted above, isoflavone supplementation or exercise training was indicated to preserved BMD in postmenopausal women; therefore, combined treatments would be additive for preserved BMD. Interestingly, results of the present meta-analysis showed that the combined therapies did not preserve BMD in any sites along with the control group. Studies have reported that isoflavone supplementation with exercise involves the different types of ERs on bone for the transduction of mechanical strains to activate osteoblasts. Exercise training may activate ER-α and promote osteoblast proliferation.[35,36] On the other hand, ER-β, termed the "anti-mechanostat", seems to down-regulate the mechanical strain on bone induced by exercise.[37,38] There is a stronger affinity for soy isoflavones to activate ER-β than for ER-α, which may reduce the detection of mechanical strains from exercise training, thereby decreasing the effectiveness of exercise loading on bone. Our present meta-analysis is not agreement with results from some animal studies,[39–41] which may be contributed to higher doses relative to body weight of soy isoflavones was administered. It is easier to elevate blood levels of isoflavones, and at these higher blood levels, two types of ERs may be activated.[42]

Our study has several strengths as follows: (1) To our knowledge, this is the first systematic review and meta-analysis including 609 postmenopausal women to comprehensively address the effects of isoflavone supplementation combined with exercise training on BMD in various sites. Only clinical trials investigating the combined treatment were included; therefore, studies that investigate either one treatment were not taken into consideration. (2) The duration of all studies ranged from 6 to 24 months; therefore, considering that the bone remodeling cycle lasts about 4–8 months, study durations would be relevant for determining BMD changes.

There are several design and methodological limitations of this study that must be considered in the interpretation of the results. First, the limited included studies and small sample size do not eliminate the possibility that the results we observed resulted from chance. Therefore, further studies with a larger sample size are required to validate our result. Second, the quality of included RCTs in this review was limited, which might have contributed to the heterogeneity that has been observed in the meta-analyses presented in this study. Third, there was a great discrepancies in study protocols (the dose of isoflavones given, and the type, mode, and application of the exercise interventions) and baseline characteristics of women studied (various comorbidities, years since menopause onset, and the genetic susceptibility) and blinding of participants or blinding of outcome assessor. Finally, we did not perform the publication bias analysis due to the small number of studies included, which is of a concern because small studies with null results tend not to be published.

In conclusion, our literature-based systematic review and meta-analysis suggests that compared with controls, interventions that combined soy isoflavone and exercise training have no statistically significant effects on attenuating BMD loss in postmenopausal women at various sites. In particular, there are no synergistic or additive roles along with either soy isoflavone or exercise training alone. However, more well-designed clinical trials with longer term soy isoflavone and exercise interventions are imperative.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://doi.org/10.1097/JCMA.0000000000000264.

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