The effect of soy isoflavones and soy isoflavones plus soy protein on serum concentration of C-reactive protein among postmenopausal women: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Evidence suggest soy isoflavones might reduce inflammatory biomarkers, therefore; the objective of this study is to conduct a systematic review and meta-analysis on randomized controlled trials (RCTs) that assessed the effect of soy isoflavones on serum concentration of C-reactive protein (CRP) among postmenopausal women. Literature search was conducted by searching PubMed, Scopus, ISI Web of Science, Cochrane Library, and Clinicaltrials.gov up to January 2020. The mean change from baseline in the CRP concentrations and its SD for both intervention and comparison groups were used to compute the effect size. The summary of the overall effects and heterogeneity was estimated by using the DerSimonian and Laird random effects model. The protocol was registered with PROSPERO (No. CRD42020166053). This article considered 23 articles for systematic review and 19 articles for meta-analysis. The overall effect suggested a non-significant effect of soy isoflavones on serum CRP concentrations (WMD= 0.08 mg/L, 95% CI: -0.08, 0.24; p=0.302) and the overall effect of the combination of soy isoflavones plus soy protein indicated non-significant effect in serum levels of CRP (WMD= -0.02 mg/L 95% CI: -0.12, 0.08; p=0.715). There was no significant change in serum levels of CRP in subgroup analysis based on dose, age, intervention duration, baseline CRP level, sample size, region, quality assessment, publication year, and health status. Dose response analysis revealed no association of higher dose of soy isoflavones with isoflavones effect on CRP levels.

Conclusion:

Published RCTs did not provide strong evidence regarding decreasing effect of soy products on serum CRP concentration among postmenopausal women.

Key words:

Soy isoflavones; Soy protein; Postmenopausal women; C-reactive protein.

Introduction:

Local inflammation starts in fourth decade of life and increases during aging (1). The enhancement of proinflammatory cytokines causes oxidative stress and results in damage to various intracellular components such as regulatory and structural proteins, DNA, and lipids (2). C-reactive protein (CRP) considers as a hepatically-produced acute phase reactant protein. Its serum concentration is associated with inflammation (3) and increased serum levels of CRP is a predictor of ischemic stroke and first myocardial infarction in humans (4, 5). According to Women's Health Study, postmenopausal women with the highest CRP concentration at baseline had a 7-fold enhancement in myocardial infarction risk and 5-fold enhancement in any vascular event (6). Thus, it seems that high serum level of CRP can predict cardiovascular events specially among postmenopausal women.

Beside the enhancement of inflammation, endogenous estrogen reduction is also a reason for cardiovascular disease (CVD) among postmenopausal women (7). Hormone replacement therapy (HRT) has favorable effects on endothelial function, antioxidant protection, blood lipids and lipoprotein concentrations, and vascular reactivity (8, 9). Despite the positive effects of estrogen therapy on clinical markers, the benefits of HRT for postmenopausal women remain controversial (10). Thus, lifestyle, cardioprotective nutrients, and selective estrogen receptor modulators, which consider as alternative to HRT, are of interest.

Polyphenolic isoflavones such as genistein and daidzein present in soy and structurally are similar to estradiol (11), therefore; they can bind to estrogen receptor β in vascular wall (12). In vitro and in vivo evidence indicated that genistein, as the predominate soy isoflavones, decreases the oxidative susceptibility of Low-density lipoprotein (LDL), inhibits tyrosine kinase (13, 14), influences vascular tissue metabolism (15), and decreases the proliferation of smooth muscle (16). Animal experiments and cell studies propose that soy isoflavones as well as the genistein or daidzein have anti-inflammatory and lipid lowering effects (17, 18). Scientists suggest soy isoflavones might reduce inflammatory biomarkers through the inhabitation of tyrosine kinase (19, 20). Beside soy isoflavones, soy protein also is recommended as a food for cardiovascular protection through its favorable impact on blood pressure and cholesterol (21, 22). Some studies have indicated that substitution of animal protein with soy protein might reduce circulating levels of inflammatory biomarkers (23, 24).

Previous information regarding soy consumption and inflammatory markers among postmenopausal women are far from conclusive. Some randomized clinical trials support the effectiveness of soy food consumption on proinflammatory cytokine reduction (25-29), while others do not (30-36). A meta-analysis in 2011 with 14 trials examined soy isoflavones effect on serum concentration of CRP among postmenopausal women and their results proposed non-significant effect of soy isoflavones on CRP (37). In meta-analysis by Dong J-Y et al., the effect of soy isoflavones and soy protein did not report separately and authors performed meta-analysis on 14 trials without considering whether participants were taking soy protein, soy isoflavones or both. Meanwhile, several new randomized clinical trials (RCTs) are published and higher dose of soy protein or soy isoflavones were used with longer intervention duration. Whether new RCTs after 2011 could change previous meta-analysis result is unknown.

Since they are new trials after year 2011, we performed an update systematic review to report a summary of RCTs exploring the effect of soy isoflavones and soy isoflavones plus soy protein on CRP and if possible performing a meta-analysis.

Material and Methods:

PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklists were used for all steps of conducting the present systematic review and meta- analysis (38). The protocol was registered with PROSPERO (No. CRD42020166053).

Literature search:

Literature search was conducted by searching PubMed (http://www.pubmed.com; National Library of Medicine), Scopus (http://www.scopus.com/), and ISI Web of Science (http://www.thomsonreuters.com), Cochrane Library (https://www.cochranelibrary.com), and Clinicaltrials.gov (https://www.clinicaltrials.gov) up to January 2020 to identify RCTs exploring the effect of soy isoflavones, soy protein or combination on CRP levels among postmenopausal women. Those data bases were searched by following related medical subject heading (MeSH) terms and non-MeSH terms for soy, CRP and clinical trial: “C-Reactive Protein”, “Protein-C Reactive”, “CRP”, “Soy Foods”, “Soy Food”, “Soy, Food”, “Soy, Foods”, “Soyfood”, “Soyfoods”, “Foods Soy”, “Soy Cheese”, “Soy Cheeses”, “Soy Sauce”, “Soysauce”, “Soy Bean Curd”, “Texturized Soy Protein”, “Texturized Soy Proteins”, “Texturized Vegetable Protein”, “Soya”, “Natto”, “Tempeh”, “Tofu”, “Miso”, “Soy Milk”, “Milk Soy”, “Milk, Soy”, “Soy Beverage”, “Soy Beverages”, “Soy, Beverage”, “Soybeans”, “Soybean”, “Soy Bean”, “Soy Beans”, “Glycine max”, “Soybean Proteins”, “Soy Bean Proteins”, “Soy Protein”, “Soy Proteins”, “Proteins Soy”, “Protein Soy”, “Genistein”, “Soy Products”, “Isoflavones”, “Isoflavone”, “Homoisoflavones”, “3-Benzylchroman-4-Ones”,

"Phytoestrogens", "Phytoestrogen", "Phyto-Estrogen", "Plant Estrogen", "Plant Estrogens", "Equol", "Clinical Trials", "Clinical Trial", "RTC". Search strategy was designed by Boolean operators, quotation marks, parentheses, and asterisks. All found papers by systematic search were exported to reference manager software (EndNote X7) and two reviewers separately checked title and abstract of exported papers in order to find relevant RCTs. Reference list of relevant reviews and RCTs were hand searched to find any other relevant RCTs. We did not have any restriction on publication time and any discrepancies were solved by consulting with third investigators (A.Gho).

Study eligibility criteria:

PICOS (Patient/Population, Intervention, Comparison, Outcome, Study types) framework was used as inclusion criteria for this systematic review and meta-analysis. Original investigations with randomized controlled trial design that conducted among postmenopausal women were considered for inclusion in this article. For inclusion, trials should report the effects of soy isoflavones or soy isoflavones plus soy protein on serum concentration of CRP as primary or secondary outcomes. After reading the full texts of retrieved clinical trials, we did not consider RCTs with following criteria in our systematic review and meta-analysis: 1) taking other nutrient supplements beside soy in intervention group; 2) trials without comparison group; 3) Not reporting information related to serum concentration of CRP at baseline or after intervention and any data for computing it; 4) Reporting serum concentration of CRP in figures; 5) Not reporting the dose of soy isoflavones and protein in natural soy product; 6) Non-English articles.

Data extraction:

Two independent authors (M.H and A.Gha) conducted data extraction and following information were extracted: the first author's name, publication year, country where RCTs were conducted, sample size, study design, age range and/or mean, soy isoflavones and soy protein dose and source, intervention duration, placebo kind, subjects health status, changes in mean of CRP and its corresponding standard deviation. Any discrepancies in this stage also were resolved through consultation with third reviewer. We converted all CRP measurements to the same unit (mg/L). Studies which had more than one intervention or comparison group were included separately.

Quality assessment:

Two reviewers separately assessed the quality of included trials by Cochrane Collaboration's tool (39). Following items are included in this tool for risk of bias assessment: I) selection bias: A) random sequence generation, B) allocation concealment; II) reporting bias; III) performance bias; IV) detection bias; IV) attrition bias. Each item was judged as "unclear risk of bias", "high risk of bias," or "low risk of bias". We considered included RCTs as good quality if it had at least low risk of bias for three criteria, "fair" if it had low risk for two criteria, and "weak" if it had low risk for less than two criteria (39).

Data synthesis and statistical analysis:

A meta-analysis was performed using mean differences (MDs) and their standard deviations (SDs) for CRP (mg/l), or these values were computed using the data were extracted from included articles. Based on Cochrane Handbook (40) the mean change from baseline in the CRP concentrations and its SD for both intervention and comparison groups were used to compute the effect size. Hozo method (41) was used to estimate mean of CRP concentrations if median or range was reported. Moreover, SDs were computed by multiplying standard errors (SEs) by square root of the sample size in studies which reported SEs. The summary of the overall effects and heterogeneity was estimated by using the DerSimonian and Laird random effects model (42), if a heterogeneity test was statistically significant. Statistical heterogeneity of intervention effects was measured using Cochran's Q test and I-squared statistic. Heterogeneity was considered substantial if p-value for the Cochran's Q test was [?]0.10 or value of the I-squared statistic was [?]50% (43).

Subgroup analyses was performed to explore sources of heterogeneity which included soy isoflavones dosage or soy isoflavones plus soy protein dosage, study design, intervention duration, mean of baseline CRP concentration, health status of participants, sample size, geographical region, age of participants, body mass index

(BMI), quality assessment of articles and year of study publication. Meta-regression was used to examine the impact of moderator variables on MDs and compute adjusted effect of soy isoflavones dosage and soy isoflavones plus soy protein dosage on MDs after controlling for other variables. Visual inspection of Begg's funnel plot, Begg's rank correlation, and Eggar's weighted regression tests were employed to evaluate the presence of publication bias in the meta-analysis (44, 45). Sensitivity analysis was conducted using the leave-one out method to specify the effect of each study on the overall effect size. Ninety-five percent confidence intervals were provided for all calculated effect sizes. All analyses were conducted using STATA 15 software (Stata Corp, Collage Station, TX).

Results:

Study selection:

Systematic search of databases retrieved 3502 articles. By removing duplicate papers, 2199 articles remained for reading title and abstract. After reading titles and abstracts, 2169 of them were excluded; 30 RCTs remained for reading full text. Seven articles were excluded due to following reasons: non-English article (n=1), using other nutrients beside soy intervention (n=5), not reporting CRP unit (n=1) (**Figure 1**). Therefore, 23 papers were eligible for this systematic review (24-36, 46-55). Since 4 articles (28, 32, 50, 55) did not report enough data for meta-analysis, 19 articles were included in meta-analysis (24-27, 29-31, 33-36, 46-49, 51-54). (**Table 1**).

Study characteristic:

Ten articles assessed the effect of soy isoflavones (27, 28, 30, 33, 34, 46-48, 51, 55), nine articles assessed the effect of soy isoflavones plus soy protein (24-26, 31, 32, 35, 50, 53, 54), and four articles assessed the effect of both soy isoflavones and soy isoflavones plus soy protein (29, 36, 49, 52). Participants in eight articles received soy isoflavones plus soy protein by taking natural soy product (24-26, 29, 31, 32, 50, 52, 54). Seven articles had two intervention groups and one comparison group (24, 26, 29, 31, 36, 49, 52) and one article had two study groups (25), therefore; we considered every article as two separate articles and separate effect sizes were calculated from each study. In three studies by Llaneza, P et al., (48), Liu Z, M et al., (36), and Aubertin-Leheudre, M et al., (30) CRP concentration reported in regular period during intervention duration, so we calculated separate effect sizes for every treatment duration which CRP concentration was reported. In total, 33 datasets (17 datasets for soy isoflavones and 16 datasets for soy isoflavones plus soy protein) from 19 studies with 1407 subjects were analyzed in our meta-analysis.

Out of twenty-three articles, nine articles had cross-over design (24-27, 35, 46, 50, 53, 54) and fourteen articles had parallel design (28-34, 36, 47-49, 51, 52, 55). Soy isoflavones dose was from 10 mg/day to 160 mg/day and treatment duration ranged from 4 weeks to 96 weeks. Regarding subjects health status, thirteen RCTs indicated soy supplements effects among healthy postmenopausal women (24, 25, 27, 29, 32-35, 49, 50, 52, 53, 55), five RCTs among obese or overweight women (28, 30, 47, 48, 51), one article among postmenopausal women with abdominal obesity (54), two RCTs on postmenopausal women with metabolic syndrome (26, 31), and two articles on patients with diabetes (46) or prediabetes (36).

Risk of bias assessment:

Out of the twenty-three RCTs included in the systematic review, one RCT scored as "weak" (24) seven RCTs scored as "fair" (25, 26, 35, 49, 50, 53, 55), and fifteen RCTs as "good" (27-34, 36, 46-48, 51, 52, 54). According to blinding of participants and personals or outcome assessors eight trials (24-26, 31, 35, 50, 53, 55) and four trials (24, 50, 53, 55) had high risk of bias respectively. Lack of allocation concealment was the source of risk of bias in five studies (24, 30, 46, 49, 50). One study and four studies had high risk of bias regarding incomplete outcome data (49) and selective reporting (24, 27, 32, 49). More details of the quality assessment of included RCTs is presented in**table 2** .

Findings from the meta-analysis:

Twelve studies with seventeen effect sizes evaluated soy isoflavones effects on serum CRP concentrations

(**Figure 2**). The overall effect suggested a non-significant effect in serum CRP concentrations after supplementation with soy isoflavones compared with comparison group (WMD= 0.08 mg/L, 95% CI: -0.08, 0.24; p=0.302). There was a substantial heterogeneity between studies (Cochrane's Q test, $p < 0.001$; I^2= 87.0%). Sensitivity analysis showed that excluding each trials from the overall analysis did not reveal a significant change in overall effect size of soy isoflavones on CRP concentration. Subgroup analysis based on all studied variables could not diminish the heterogeneity between studies (**Table 3**). Subgroup analyses revealed no significant change in circulatory levels of CRP following soy isoflavones intake compared with comparison group in any of the subgroups.

The overall effect of soy isoflavones plus soy protein on serum CRP is shown in **Figure 3** . Eleven studies with sixteen effect sizes assessed the effect of soy protein and soy isoflavones combination on serum CRP levels. The overall estimates indicated non-significant effect in serum levels of CRP following soy isoflavones plus soy protein intake in comparison with control group (WMD= -0.02 mg/L 95% CI: -0.12, 0.08; p=0.715) with high heterogeneity (Cochrane's Q test, $p <0.001$, I^2= 84.9%). Sensitivity analysis showed that excluding each trials from the overall analysis did not reveal a significant change in overall effect size of soy isoflavones plus soy protein on CRP concentration. The between-group heterogeneity was not significant in trials using soy isoflavones >100 mg/d (Cochrane's Q test, p=0.600, I^2=0.00%), in trials with parallel design (Cochrane's Q test, p=0.074, I^2=53.7%), in trials performed with study duration>56 day (Cochrane's Q test, p=0.074, I^2=47.9%) and in trials conducted in healthy people (Cochrane's Q test, p=0.330, I^2=13.2) (**Table 4**). In subgroup analysis based on BMI indicated that soy isoflavones plus soy protein could increase CRP levels in people with BMI[?]26 (WMD= 0.36 mg/L 95% CI: 0.01, 0.72; p=0.045, I^2=65.8%), but a non-significant reduction was observed in people with BMI>26 (WMD= -0.08 mg/L 95% CI: -0.18, 0.02; p=0.121, I^2=91.3%) (**Figure 4**). However, in subgroup analysis revealed no significant change in circulatory levels of CRP following soy isoflavones plus soy protein intake compared with comparison group in other subgroups (**Table 4**).

Meta-regression analysis and publication bias:

Meta-regression analysis was used to explore possible sources of heterogeneity and to find characteristics of participants or trials with effective treatment effects. The result of univariate meta-regression analysis didn't show a significant linear association between soy isoflavones dose and effect size of soy isoflavones effect on CRP levels (Coefficient= -0.0004, 95% CI: -0.03, 0.03; P=0.977) (**Table 5**& **Figure 5**). Also, after adjustment for design, intervention duration, baseline CRP, health status, sample size, region, age, BMI, quality assessment, and publication year of article, dose of soy isoflavones did not have any linear association with effect size of soy isoflavones effect on CRP levels (Coefficient= 0.009, 95% CI: -0.11, 0.13; P=0.847). We also didn't find a significant association between other studied variables and effect size in univariate meta-regression analysis (**table 5**). Regarding RCTs which indicated soy isoflavones effect, there was not any evidence of publication bias (Egger test p-value=0.954) (**Figure 6**).

Although, univariate meta-regression analysis didn't show a significant linear association between soy isoflavones dose of combination of soy isoflavones plus soy protein dose and studied effect size (Coefficient= -0.008, 95% CI: -0.02, 0.001; P=0.082) (**Table 6 & Figure 7**). Also, after adjustment for other variables, there was not observed any significant association between dose of soy isoflavones and studied effect size (Coefficient= -0.005, 95% CI: -0.02, 0.01; P=0.447). Although the funnel plot was not visually symmetric for studies included in meta-analysis of soy isoflavones plus soy protein (**Figure 8**), the results from the Egger test did not show evidence of publication bias (Egger test p-value=p=0.781).

Discussion:

To the best of our knowledge this is the first meta-analysis which reported the effect of soy products based on soy isoflavones and the combination of soy isoflavones plus soy protein on serum CRP levels among postmenopausal women.

Our systematic review contains 23 articles studying the effects of soy isoflavones and soy isoflavones plus soy protein on serum CRP concentration. Meta-analysis contains 19 articles with 33 datasets and its results

indicated that soy isoflavones and soy isoflavones plus soy protein could not change CRP concentration among postmenopausal women. Our meta-analysis results confirm the result of a meta-analysis in year 2011(37) which reported the effect of overall soy products, furthermore; this results revealed that new published papers with longer treatment duration, using higher dose of soy isoflavones or soy protein, and more sample size could not change non-significant effect of soy products on serum CRP levels in previous article.

There was no significant change in serum levels of CRP in subgroup analysis based on dose, age, intervention duration, baseline CRP level, sample size, region, quality assessment, publication year, and health status. Dose response analysis revealed no association of higher dose of soy isoflavones with isoflavones effect on CRP levels.

Review articles revealed that some nutrients might change inflammatory mediators (56, 57). Evidence from in vitro (58) and animal studies (59) have indicated that soy products can reduce the activity of nuclear factor-kB as cytokine-induced signal transduction thereby decreases the concentration of pro-inflammatory cytokine. Furthermore, new evidence suggested that IL-6 by activating nuclear factor-kB is able to induce hs-CRP expression (60). Therefore, in participants with health condition which enhances IL-6 levels, soy products by inhibition of IL-6 effect on nuclear factor-kB and CRP expression can reduce CRP levels, but this results were not confirm in our meta-analysis.

Regardless of subgroup analysis, one of the main reasons for non-significant effect of soy isoflavones or the combination of soy isoflavones and soy protein on serum CRP levels might be due to different ability of participants in the metabolization of isoflavones to equol (61). Equol is an isoflavandiol estrogen produced from daidzein by bacterial flora in the intestines (61). Although equal has the superior antioxidant activity in compared with other isoflavones, most people do not have ability to produce equol. In western countries 20-25% of papulation have the capacity to produce equol and in Asian countries about 60% of populations produce equol (62). The result of univariate meta-regression analysis showed there is a significant association between region and soy isoflavones effect on serum CRP levels.

In a study by Acharjee et al., (25) revealed that taking soy products causes no significant changes in blood CRP levels among equol non-producers women, but equol-producers indicated significant reduction. Most articles in our meta-analysis did not report any information regarding equol production in participants and we could not perform subgroup analysis based on equol non-producers and equol-producers.

According to scientific proposal, soy products might be more effective among Asian papulation, but our analysis revealed non-significant changes in CRP levels in subgroup analysis based on region. One possible reason for this result might be participants age in this meta-analysis. Subjects in our article were postmenopausal women and intestinal microflora changes during aging might be a reason for low amount of equal production in intestine, therefore; soy isoflavones fail to exert anti-inflammatory effects. (63)

There was a considerable heterogeneity between included studies even in most subgroup analysis. The probable reasons might be related to discrepancies in the ability of study papulation in metabolization and absorption of isoflavones, participants' intestinal flora, dietary habit and genetic background of the participants.

Our systematic review and meta-analysis has several limitations. First of all, most articles did not have any information related to equal production among participants, therefore; we did not assess whether equal production could change non-significant effect of soy products on CRP to significant effect among elderly subjects. Secondly, participants' dietary habit was not reported in any article. Since dietary habit might change intestinal flora, neglecting confounding effect of dietary habit is an important issue. Thirdly, most articles did not have any information regarding drugs used by participants. Fourthly, trials included in this meta-analysis had small or moderate sample size. Small sample size does not have enough statistical power to detect a significant effect in trials and in the meta-analysis. Fifthly, even though changes in fat mass are very important factor in inflammatory mediators levels, most RCTs did not report any information related to body composition changes. Sixthly, we did not include non-English articles.

Our meta-analysis had a number of strengths in comparison with previous meta-analysis. First of all, the large number of studies were included in meta-analysis, therefore; we could conduct subgroup analysis based on dose, age, intervention duration, baseline CRP level, sample size, region, BMI, quality assessment, and publication year. Secondly, we included RCTs which used only soy products in form of supplements or natural soy products and we excluded studies with other food supplements beside soy products. Thirdly, our meta-analysis included 19 trials from different countries; therefore, we might limit the differences in habits and lifestyles in this analysis. Fourthly, we reported the effect of soy isoflavones or the combination of soy isoflavones and soy protein separately with sufficient effect sizes. Fifthly, we did not any limitation on publication time. Finally, Egger's test revealed no evidence of significant publication bias.

In conclusion according to our results, published RCTs did not provide strong evidence regarding decreasing effect of soy isoflavones or the combination of soy isoflavones plus soy protein on CRP concentration among postmenopausal women. Future studies should report soy effect among equal producers and non-producers and assess gut microbial composition; furthermore, confounding effect of diet should be adjusted.

Conflict of interest:

No conflict of interest

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