Effect of oral isoflavone supplementation on vascular endothelial function in postmenopausal women: a meta-analysis of randomized placebo-controlled trials

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CRD summary
This review concluded that oral isoflavone supplementation significantly improved endothelial function in postmenopausal women with low baseline flow-mediated dilation values, but not in those with high baseline values. Although the review methods were good, the conclusion should be treated with caution as it was based on a small number of heterogeneous studies.

Authors' objectives
To evaluate the effect of oral isoflavone supplements on endothelial function in postmenopausal women.

Searching
PubMed, EMBASE and The Cochrane library were searched from inception to March 2009. Search terms were reported. Reviews and reference lists of relevant articles were searched. Only published studies were included.

Study selection
Double-blind randomised placebo-controlled trials of oral isoflavone supplementation that measured endothelial function using flow-mediated dilation (FMD) were eligible for inclusion. Isoflavone treatment had to last for at least three days.

Study participants were mostly healthy postmenopausal women; two studies were in hypercholesterolaemic postmenopausal women. Mean age ranged from 55.4 to 66.7. Mean baseline cholesterol ranged from 180 to 286mg/dL. Mean baseline FMD ranged from 2.1% to 9.6%. Isoflavone was provided as soy protein or in tablets with doses that ranged from 50 to 99mg/day. Treatment duration ranged from two weeks to 12 months.

Studies were selected independently by two reviewers.

Assessment of study quality
Study quality was assessed using the criteria: quality of randomisation and generation of the sequence; allocation concealment; blinding; and reporting of withdrawals. The maximum possible quality score was 5.

Two reviewers independently performed the quality assessment.

Data extraction
The percentage change in FMD between baseline and final assessments was either extracted or estimated using methods reported in the Cochrane Handbook for Systematic Reviews.

Two reviewers independently performed data extraction.

Methods of synthesis
Weighted mean differences (WMD) and 95% confidence intervals (CI) were obtained from a random-effects model. Statistical heterogeneity was assessed using Cochran’s Q test (p<0.1) and I². Heterogeneity was considered significant where I² values were over 50%. Univariate meta-regression and subgroup analyses were used to explore sources of heterogeneity and these considered age, duration of supplementation, source and dose of oral isoflavone, baseline cholesterol concentration and age-adjusted baseline FMD levels. Publication bias was assessed using funnel plots and the Egger test.
**Results of the review**

Nine studies (n=440, sample size range 18 to 202) were included. Quality scores ranged from 3 to 5 (out of five). All studies were randomised, double-blind and placebo-controlled. Six studies reported details of withdrawals. Five were cross-over studies.

Isoflavone supplementation resulted in greater changes in FMD levels compared with placebo (WMD 1.75%, 95% CI 0.83 to 2.67%; nine studies), although there was very high heterogeneity (I²=92%).

Metaregression and subgroup analyses showed that most of the heterogeneity in the outcome was explained by age-adjusted baseline FMD levels; studies with low baseline values (≤5.2%) had a greater change in FMD in isoflavone groups (WMD 2.22%, 95% CI 1.15 to 3.30). Significant heterogeneity remained (I²=96%). For studies with high baseline FMD levels, there was no significant difference between isoflavone and placebo. Isoflavone source, dose, duration of treatment and baseline cholesterol concentration did not have any effect on the outcome.

There was no evidence of publication bias.

**Authors’ conclusions**

Oral isoflavone supplementation significantly improved endothelial function in postmenopausal women with low baseline flow-mediated dilation values (<5.2%), but did not improve endothelial function in women who had high baseline values.

**CRD commentary**

This review had a clear research question and inclusion criteria. Only published studies were included and it was unclear if there were any language restrictions; however, no evidence of publication bias was found. Study quality was assessed. Inclusion criteria restricted studies to a specific design; no quality details were presented on an individual study basis. Methods of meta-analysis were appropriate, but given the high observed heterogeneity pooling the data may not have been the best option. The authors explored reasons for the heterogeneity and their conclusion was based on a subgroup analysis, albeit still based on very heterogeneous results. Although the methods of this review were good, the conclusion should be treated with caution as it was based on a small number of heterogeneous studies.

**Implications of the review for practice and research**

**Practice:** The authors stated that the baseline endothelial profile may be an important factor influencing the effects of oral isoflavone supplementation.

**Research:** The authors stated that high-quality studies in women with cardiovascular disease and in men and people with hypercholesterolaemia were needed to confirm these results and explore the exact mechanisms of isoflavone in improved endothelial function. Research was needed on the effects of different sources of isoflavone on endothelial function.

**Funding**

National High-Tech Research and Development Program of China (grant no. 2006AA02A406).

**Bibliographic details**


**PubMedID**

19923372

**DOI**

10.3945/ajcn.2009.28203
Original Paper URL
http://www.ajcn.org/cgi/content/abstract/91/2/480

Indexing Status
Subject indexing assigned by NLM

MeSH
Cardiovascular Diseases /prevention & control; Dietary Supplements; Endothelium, Vascular /drug effects; Female; Humans; Isoflavones /administration & dosage; Middle Aged; Placebos; Postmenopause /drug effects; Randomized Controlled Trials as Topic; Vasodilation /drug effects

AccessionNumber
12010001506

Date bibliographic record published
19/05/2010

Date abstract record published
29/09/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.