Effect of long-term intervention of soy isoflavones on bone mineral density in women: a meta-analysis of randomized controlled trials

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CRD summary
The review evaluated the effectiveness of long-term soy isoflavones on bone mineral density in women and found that there was no significant benefit for the femoral neck and unlikely to be a benefit for the lumbar spine and hip. The reliability of the authors' conclusions is unclear due to uncertainties around the review methodologies and large between-study heterogeneity.

Authors' objectives
To evaluate the effectiveness of long term soy isoflavones on bone mineral density in women.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from January 1990 to March 2008 for publications in English. The bibliography of each retrieved article and review was handsearched. Only full-length articles were considered. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) of soy isoflavone supplementation in adult females that reported bone mineral density (mg/cm²) at the lumbar spine, total hip or femoral neck as the primary outcome were eligible for inclusion. Eligible studies measured bone mineral density by dual X-ray absorptiometry (DXA). Study duration needed to be at least one year. RCT design of eligible studies had to be either parallel or cross-over and have a parallel control group. The difference in intervention between treatment and control groups had to be soy isoflavones, soy foods or products that provided soy isoflavones only. Studies had to provide details of dose of supplemental isoflavones. Studies had to report standard deviation (SD), standard error or 95% confidence intervals (CI) by treatment groups.

Studies were excluded if they were duplicated reports or a subgroup analysis of the same study. Weighted mean dose of isoflavones in the included studies was 87mg/day (range 40 to 200mg/day). Soy isoflavone sources were either isolated soy protein that contained isoflavones, actual isoflavones or soya milk. Isoflavone dose in control groups in most included studies was 0 (range 0 to 4mg/day). Duration of most studies was 12 months (range 12 to 24 months). Most patients in included studies were postmenopausal women. Mean age ranged from 24 to 67 years. Most of the included studies had no bone mineral density criteria for enrolment of participants.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Methodological quality was assessed using the method developed by Jadad and Schulz. This included a three-item checklist that assessed: bias and randomisation (0 to 2 points); blinding (0 to 2 points); and withdrawals/dropout (0 to 1 point). Possible quality score ranged from 0 to 5. Jadad scores for individual studies and further details were reported.

The authors described neither how validity assessment was performed nor how many reviewers performed the assessment.

Data extraction
Data that related to study design, participants, interventions and the mean (with standard deviation) of the baseline and endpoint bone mineral densities or their changes were extracted. Mean differences in net changes, and 95% confidence intervals (CI), were calculated. Results for the longest duration were used for studies with multiple endpoints.
Data were extracted independently by two reviewers using a standard form; minor discrepancies were resolved by authors’ discussion.

**Methods of synthesis**

Pooled weighted mean differences (WMDs) and 95% CIs were calculated based on the calculated reciprocal of the variance for each study using fixed-effect and random-effects models. A random-effects model was used if statistical heterogeneity was identified using the Q statistic and I² tests. Publication bias was assessed using the method of Egger et al. and visually using funnel plots. Where publication bias was detected, the fail-safe number method was used to assess its effect. Sensitivity analyses were carried out by limiting analyses to postmenopausal women or high-quality studies (Jadad score of 4 or more). Additional prespecified subgroup analyses were carried out stratified by: intervention dose; isoflavone pills compared with isoflavones in soy protein or soy foods; and ethnic difference.

**Results of the review**

Ten relevant RCTs were identified (n=896). All were parallel RCTs and all but one were double blind. The study size weighed mean Jadad score was 4.1 (standard deviation 1.0). All RCTs except one reported that there were no significant differences in baseline characteristics between intervention and control groups.

A mean dose of 87mg/day soy isoflavones did not significantly effect bone mineral density changes at the lumbar spine, total hip or femoral neck using a random-effects model or a fixed-effect model. There was significant between-study heterogeneity in effects of soy isoflavones on bone mineral density changes at the lumbar spine (I²=70%) and femoral neck (I²=59%), but not for the total hip (I²=0%).

Subgroup analyses to explore sources of heterogeneity found no significant differences in pooled effects between various subgroups stratified by intervention doses (<80mg/day versus ≤80mg/day), isoflavone source (soy protein versus isoflavone extract) or ethnic difference (Asian versus Western). A larger dose (≥80mg/day), but not a lower dose (<80mg/day) of isoflavone had a weak beneficial effect on lumbar spine bone mineral density (WMD 6.0mg/cm²/year, 95% CI -0.7 to 12.7, p=0.08).

Sensitivity analyses found that pooled effects were similar when analyses were limited to postmenopausal women and to higher-quality studies. For all pooled analyses, only one subgroup analysis showed evidence of publication bias (isoflavone dose of ≥80mg/day, p=0.05 for publication bias).

**Authors’ conclusions**

Soy isoflavone supplementation was unlikely to have a significant favourable effect on bone mineral density at the lumbar spine and hip in women.

**CRD commentary**

The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched. Only studies published in English were searched for and it appeared that unpublished studies were not considered; therefore, some relevant studies may have been missed. An assessment of publication bias only found very limited positive evidence. Study quality was assessed using suitable criteria. Relevant study details were reported, but no specific details of loss to follow-up were given. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for meta-analysis of RCTs seemed appropriate. A sensitivity analysis was carried out. Data extraction was carried out with efforts to reduce error and bias, but it was not reported whether such a process applied to other aspects of the review process and this made it difficult to assess the likelihood of error and bias in study selection and validity assessment. The extent to which the authors’ conclusions were reliable is unclear due to uncertainties surrounding the review methodologies and the presence of large between-study heterogeneity.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors did not state any implications for research.
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