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FILE: ▪Red Clover (*Trifolium pratense*)
▪Isoflavones
▪Osteoporosis

HC 010765-307

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RE: Red Clover Isoflavones May Protect Against Osteoporosis in Women

Atkinson C, Compston JE, Day NE, Dowsett M, Bingham SA. The effects of phytoestrogen isoflavones on bone density in women: a double-blind, randomized, placebo-controlled trial. *Am J Clin Nutr*. 2004 Feb;79(2):326-33.

Supplementation with plant-derived isoflavone phytoestrogens is an alternative to conventional hormone replacement therapy (HRT) for those seeking to avoid the side effects of HRT. However, HRT does have a positive effect on bone density and body composition in postmenopausal women who are prone to osteoporosis. According to the authors, the effect of isoflavone phytoestrogens on bone density is not well studied.

In this double-blind, randomized, placebo-controlled clinical trial, researchers attempted to determine the effect of an isoflavone supplement derived from red clover (*Trifolium pretense*) on bone density in women aged 49-65. The subjects were women (n=205) recruited from the Breast Cancer Screening Unit of Addenbrooke's Hospital (Cambridge, England, United Kingdom). The subjects were randomly assigned to the placebo group (n=103) or the isoflavone group (n=102). Women with a history of breast cancer and women taking HRT were excluded from the study. The isoflavone group received 1 tablet/day of Promensil™, an isoflavone extract derived from red clover that is standardized to 26 mg biochanin A, 16 mg formononetin, 1 mg genistein, and 0.5 mg daidzein (Novogen Ltd., Sydney, Australia). The placebo was identical in appearance to Promensil, and all participants and researchers were blinded. The clinical trial lasted 1 year, and 86 subjects in the isoflavone group and 91 subjects in the placebo group completed the trial. Sixteen women withdrew from the isoflavone group and 12 from the placebo group, principally because of work commitments or family problems, but also because of feeling no beneficial effect of the intervention, having no interest in continuing on the trial, heavy menstrual bleeding, or illnesses preventing completion of study activities; the difference between treatment group withdrawals was not significant (χ^2 =1.123, P=0.29). Subjects gave blood and urine samples, completed food frequency questionnaires, and were given bone density and body composition tests.

The placebo group and the isoflavone group were not significantly different at baseline. Dietary intake of calcium and vitamin D during the 12-month study period was not significantly different between the 2 groups. Women in the isoflavone group showed less lumbar spine bone loss than women in the placebo group. Spine bone mineral content (BMC) decreased by -1.42 ± 0.36% for the isoflavone group and by -2.35 ± 0.37% for the placebo group (P=0.07). Spine bone mineral density (BMD) decreased by -1.08 ± 0.27% in the isoflavone group and by -1.86 ± 0.29% in the placebo group (P=0.05). Differences between the 2 groups in hip BMC and BMD were not significant. There was no significant difference between the 2 groups in change in concentrations of the *N*-propeptide of collagen type I (PINP), a marker of bone formation. However, for post-menopausal women, changes in PINP were significantly different between the 2 groups. In the isoflavone group, PINP increased 9.72 ± 25.19 mg/L and PINP decreased in the placebo group by -1.40 ± 19.12 mg/L (P=0.01). Changes in plasma-specific alkaline phosphatase (bone ALP), another marker of bone formation, were significantly different between the 2 groups for post-menopausal women, but not for the 2 groups overall. Among postmenopausal women, changes in bone ALP were 5.65 ± 5.92 and 3.71 ± 2.92 U/L for the isoflavone and placebo groups, respectively (P=0.04). No other significant differences were observed.

Researchers observed "an attenuation of lumbar spine bone loss among women taking the isoflavone supplement compared with that among women taking the placebo." They did not observe a similar attenuation in hip bone loss, but comment that this may be due to slower bone turnover in the hip and lower measurement precision. In addition, the researchers observed an increase in two markers of bone formation among post-menopausal women in the isoflavone group. The authors conclude that the red clover isoflavone supplement may have a protective effect on the lumbar spine in women. Long-term studies on the effect of isoflavones on bone density and fracture rates are needed.

—Marissa Oppel, MS

The American Botanical Council has chosen not to reprint the original article.