Effects of specific post-menopausal hormone therapies on bone mineral density in post-menopausal women: a meta-analysis

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CRD summary
This review assessed the effects of hormone therapy on bone mineral density in postmenopausal women. The authors concluded that all estrogen preparations appeared to have similar effects on maintaining bone mineral density. Since the treatments were not directly compared, the conclusions are not definitive.

Authors' objectives
To assess the effects of postmenopausal hormone therapy (pHT) on bone mineral density (BMD) in postmenopausal women.

Searching
MEDLINE and EMBASE were searched for studies published in English between 1990 and December 2002; the search terms were stated. The references in identified reports and known reviews of osteoporosis were also reviewed. Abstracts were excluded.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that lasted at least 2 years and recruited at least 60 women were eligible for inclusion.

Specific interventions included in the review
Studies of any estrogen, any progestin, or any estrogen plus any progestin (with or without calcium supplements or dietary counselling about calcium or vitamin D) compared with placebo and/or calcium or no treatment were eligible for inclusion. The studies had to be aimed at preventing postmenopausal osteoporosis. The included studies used 48 different pHT regimens; most used oral preparations. They used different approved doses of conjugated equine estrogens, estradiol, estradiol valerate, esterified estrogens, estrone sulphate, estriol, transdermal estradiol, and ethinyl estradiol or tibolone. The progestins used in combination with estrogens were medroxyprogesterone acetate, levonorgestrel, cyproterone acetate, norethisterone (norethindrone) acetate, desogestrel and norgestrel.

Participants included in the review
Studies in postmenopausal and/or ovariectomised women were eligible for inclusion, regardless of prior fracture history. The classification of women as postmenopausal in the primary studies was accepted. Most of the women in the included studies were aged 50 to 60 years (range: 40 to 76). Most studies were conducted in early-menopausal women with both ovaries, while some included postmenopausal women with hysterectomy and/or bilateral oophorectomy. Some studies did not report whether women who had a surgical menopause were included. The majority of the studies were of Caucasian women.

Outcomes assessed in the review
Studies that reported changes in BMD of the lumbar spine and/or the hip were eligible for inclusion. The outcome of interest was the mean change in BMD from baseline. The most common method of measuring BMD in the included studies was dual-energy X-ray absorptiometry; other methods included dual-photon absorptiometry and single-energy quantitative computed tomography. Studies that measured BMD using roentgenograms, metacarpal measurements, or ultrasound were excluded. The time of the outcome measurement ranged from 2 to 10 years.

How were decisions on the relevance of primary studies made?
Two reviewers selected the studies. It was unclear if this was done independently.
Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers extracted the data and the data extraction was double-checked. Data on the characteristics of the population and treatments, sample size and drop-outs were extracted. The outcome data were extracted as reported in the primary studies, or were estimated from graphs. Where possible, the data were extracted on an intention-to-treat basis. For each study with sufficient data, the mean percentage change in BMD at the femoral neck, hip and lumbar spine on treatment relative to the control group was extracted.

Methods of synthesis
How were the studies combined?
The studies were grouped a priori according to the pHT intervention and were combined within those groups using a meta-analysis. Meta-analyses were performed without individual study weighting, weighting by sample size and weighting by the ratio of sample size to drop-outs. The pooled mean change in lumbar and femoral BMD, together with the 95% confidence interval (CI), was calculated using a random-effects model. The minimum and maximum change in BMD was also calculated for each pHT group.

How were differences between studies investigated?
Separate meta-analyses were conducted for the following predetermined pHT groups: conjugated equine estrogens; estradiol, estradiol valerate, esterified estrogens, estrone sulphate and estriol; transdermal estradiol; ethinyl estradiol and tibolone. Differences between these groups were tested using an analysis of variance (ANOVA). The relationship between the mean age of the participants and the change in BMD was tested using Spearman's rank order correlation.

Results of the review
Thirty-nine RCTs were included (see Results of the Review for the number of women used in the analysis of each drug class).

The results focused on treatment effects at 2 years.

There were no apparent differences in changes in lumbar spine BMD between the various predetermined treatment groups. Almost all treatment regimens at least maintained or increased lumbar spine and hip BMD at 2 years. The results were similar for analyses adjusting for sample size and drop-outs.

Tibolone appeared to be as effective as any other estrogen regimen (ANOVA P=0.944).

Change in BMD at lumbar spine at 2 years. Analyses weighted by the ratio of sample size to drop-outs.

Conjugated equine estrogens (11 RCTs, more than 1,927 women): the mean change in BMD was 0.076 (95% CI: 0.062, 0.091).

Estradiol, estradiol valerate, esterified estrogens, estrone sulphate and estriol (11 RCTs, more than 2,004 women): the mean change in BMD was 0.072 (95% CI: 0.055, 0.089).

Transdermal estrogens (7 RCTs, 1,047 women): the mean change in BMD was 0.075 (95% CI: 0.063, 0.088).

Tibolone (5 RCTs, 1,150 women): the mean change in BMD was 0.064 (95% CI: 0.030, 0.099).

Ethinyl estradiol (1 RCT, 1,265 women): the mean change in BMD was 0.078 (95% CI: 0.047, 0.110).

There were insufficient data to compare the effects of these classes of pHT on femoral neck or hip BMD, or to compare the effects of adding progestins to a specific estrogen.
There appeared to be a trend towards reduced BMD change with increasing age, but this was not statistically significant (P=0.0962).

**Authors’ conclusions**  
All oral and non-oral estrogens appeared to have similar effects on BMD. Tibolone had a similar size of effect on BMD as the other estrogens reviewed.

**C****RD commentary**  
The review question was clear in terms of the study design, intervention, participants and outcomes. By limiting the included studies to those in English and listed in only two databases, the authors might have omitted some relevant studies. The authors acknowledged that one of the limitations of the review was the lack of an assessment of publication bias. No attempt to locate unpublished studies was reported, thus raising the possibility of publication bias. It was not stated whether the studies were selected independently by the two reviewers, so the potential for bias and errors cannot be assessed. Only RCTs were included, but their quality was not assessed further.

Information on the included studies was tabulated. Meta-analyses were performed regardless of heterogeneity. It is difficult to judge whether pooling was appropriate because no meta-analysis graphs were shown. The conclusion regarding the relative effect of different pHT treatments on BMD was based on comparisons between subgroups of trials rather than on direct comparisons within trials. Therefore, any conclusions drawn about the relative effects of hormone treatments on BMD are not definitive.

**Implications of the review for practice and research**  
The authors did not state any implications for practice or further research.

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