Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials
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Authors' objectives
To systematically review all the randomised controlled trials (RCTs) of hormone replacement therapy (HRT) that have collected nonvertebral fracture data, but may not have focused on fracture prevention.

Searching
Recent systematic reviews were used to identify HRT literature published before 1997 along with a review of the effects of HRT on cardiovascular events. MEDLINE, EMBASE, the Science Citation Index, and the Cochrane Controlled Trials Register were searched from 1997 to December 2000, using the following search terms: 'HRT, ERT, hormon* replacement'; '(o)estrogen replacement'; '(o)estradiol'; '(o)estrone'; and 'dien(o)estrol'. The authors of all trials since 1990 were contacted to establish whether fracture data had been collected. In addition, researchers in the field and pharmaceutical companies were contacted for unpublished studies.

Study selection
Study designs of evaluations included in the review
RCTs of at least 12 months' duration were eligible for inclusion. Unblinded trials were also included. The duration of the studies ranged from 12 to 120 months.

Specific interventions included in the review
Comparisons of HRT with inactive placebo, no treatment or calcium supplementation with or without vitamin D therapy were eligible for inclusion. The following types of oestrogen were used in the included studies: mestranol (20 mg orally); estradiol (1 to 2 mg orally or 0.025 to 50 mg transdermally); esterified oestrogen (0.3 to 1.25 mg orally); conjugated oestrogen (0.3 to 1.25 mg orally); and oestradiol valerate (2 mg orally). The cointerventions included progestin with and without calcium.

Participants included in the review
Women were eligible for inclusion. The included studies involved the following: healthy postmenopausal women; healthy women with hysterectomy, with and without bilateral oophorectomy; women with normal or low bone mineral density; women with established osteoporosis, coronary artery disease, or hysterectomy and Alzheimer's disease; and women with primary hyperparathyroidism. The mean age of the women ranged from 50 to 75 years across the studies.

Outcomes assessed in the review
Studies that reported or had available nonvertebral fracture data were eligible for inclusion. Fractures could be at any site other than the spine, and could be due to any cause. Studies that only reported vertebral fractures were excluded.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Study validity was assessed using the criteria developed by Jadad et al. (see Other Publications of Related Interest). These included the method of randomisation, concealment allocation, and reporting of withdrawals and drop-outs. Both reviewers assessed validity, and any disagreements were resolved by discussion.

Data extraction
Two reviewers extracted the data independently, and any disagreements were resolved by discussion.

The following data were tabulated: the author and year of publication; study duration; study population; age; type of oestrogen; use of progestin; and outcome measures.

Methods of synthesis
How were the studies combined?
A pooled relative risk (RR) of fracture was estimated, along with the 95% confidence interval (CI) using a random-effects model. The possibility of publication bias was examined using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Q statistic. Subgroup analyses were also conducted to examine the following:

- the effect of age (mean age less than 60 years versus a mean age greater than 59 years) on effectiveness;
- the effect of treatment length (less than 3 years versus greater 3 years); and
- any differential effect of HRT by fracture type.

Sensitivity analyses were conducted to compare the effect sizes of published and unpublished studies, and to examine the influence of each study on the result.

Results of the review
Twenty-two RCTs (8,774 women) were included.

There was a significant reduction in nonvertebral fractures in women who received HRT (RR 0.73, 95% CI: 0.56, 0.94, p=0.02). There was no evidence for statistical heterogeneity (chi-squared 26.42, d.f.=21, p=0.19).

The effect was greatest among women on HRT with a mean age less than 60 years (RR 0.67, 95% CI: 0.46, 0.98, p=0.03). Among women with a mean age of at least 60 years, there was a reduced but non statistically-significant effect (RR 0.88, 95% CI: 0.71, 1.08, p=0.22).

The effectiveness of HRT appeared more marked for hip and wrist fractures alone (RR 0.60, 95% CI: 0.40, 0.91, p=0.02), particularly for women aged younger than 60 years (RR 0.45, 95% CI: 0.26, 0.79, p=0.005). A longer trial duration did not produce an enhanced effect. The quality of the trials was generally good. Eleven RCTs reported the method of randomisation, 15 RCTs were reported as double-blind, and 15 RCTs reported on the withdrawals and gave reasons for them.

There was some evidence for publication bias, with unpublished trials tending to be smaller with effect sizes closer to null. There was no statistically-significant difference between the RRs of fracture for published and unpublished data. Restricting the analysis to only double-blind RCTs did not materially alter the estimate of effect.

Authors' conclusions
The review suggested that HRT reduces the incidence of nonvertebral fractures; this benefit is possibly attenuated when HRT is begun after the age of 60 years.

CRD commentary
The aims were stated and the inclusion criteria were defined in terms of the study design, participants, intervention and outcome. This was a clearly written and presented review. Several relevant sources of literature were searched and the keywords were stated. In addition, attempts were made to locate unpublished material and publication bias was assessed using a funnel plot. However, it was unclear whether any language restrictions had been applied, and the methods used...
to select the studies were not reported.

The included studies were restricted to RCTs, and study validity was assessed using the criteria of Jadad et al. (see Other Publications of Related Interest). Relevant data were extracted and tabulated, and the methods used to extract the data and assess validity were described. Statistical heterogeneity was assessed prior to the data being pooled. Sensitivity analyses were conducted to examine the influence of various factors on the outcome.

The evidence presented supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that HRT may reduce the incidence of nonvertebral fractures, and this benefit may be attenuated when HRT is begun after the age of 60 years.

Research: The authors state that RCTs are urgently required to examine the effectiveness of HRT for preventing fractures in older women, i.e. those starting HRT when aged 60 years or older.

Bibliographic details

PubMedID
11401611

Original Paper URL
http://jama.ama-assn.org/

Other publications of related interest

This additional published commentary may also be of interest. A meta-analysis of hormone replacement therapy for fracture prevention [letters]. JAMA 2001;286:2096-7.

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Estrogen Replacement Therapy; Female; Fractures, Bone /epidemiology; Humans; Middle Aged; Randomized Controlled Trials as Topic

AccessionNumber
12001008269

Date bibliographic record published
31/07/2002

Date abstract record published
31/07/2002

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.