Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women

CRD summary
The authors concluded that hormone-replacement therapy reduced a number of components of the metabolic syndrome in diabetic and non-diabetic postmenopausal women. However, oral agents presented certain adverse effects on C-reactive protein and protein S. A number of limitations, such as uncertainty regarding the quality of the included studies and the poor reporting of review methodology, limit any robust conclusions.

Authors' objectives
To examine the effects of hormone-replacement therapy (HRT) on components of the metabolic syndrome in diabetic and non-diabetic postmenopausal women.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane CENTRAL Register were searched from April 1966 to October 2004; the search terms were not reported.

Study selection
Randomised controlled trials (RCTs) comparing HRT with placebo or no hormone therapy, with a treatment duration of at least 8 weeks, in postmenopausal women were eligible for inclusion. Crossover trials with a treatment duration of less than 12 weeks were required to include a 4-week washout period. Studies reporting measures of the metabolic syndrome were eligible for inclusion. Such measures included abdominal obesity (lean body mass, waist circumference, abdominal fat), insulin resistance and diabetes (fasting glucose, fasting insulin, new-onset diabetes), lipids and lipoproteins (high- and low-density lipoprotein cholesterol, triglyceride, lipoprotein(a)), blood-pressure, inflammatory components (C-reactive protein, E-selectin) and thrombotic components (fibrinogen, plasminogen activator inhibitor-1, or protein C or S). The included studies assessed the following forms of HRT in diabetic and non-diabetic postmenopausal women: conjugated equine oestrogen, oral esterified oestrogens or transdermal oestrogen, alone or in combination with a progestin, administered as a low (0.625 mg) or high (1.25 mg) dose. The controls included placebo, calcium supplementation or no treatment. The mean treatment duration was 1 year and 6 months (range: 0.15 to 5 years). The mean baseline age was 60.3 years for women receiving HRT and 61.5 years for controls. The included studies also reported measures of intercellular adhesion molecule, vascular cell-adhesion molecule, factor VII, tissue plasminogen activator, antithrombin III and von Willebrand factor.

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Validity was assessed using the following criteria: randomisation and allocation concealment; blinding of the patients and investigators; and the reporting of drop-out rates and use of intention-to-treat analysis. The studies were evaluated separately and each criterion was assessed using a 3-point scale.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
Two investigators extracted the data on each outcome for non-diabetic women, but only data on fasting glucose and fasting insulin for women with diabetes. Dichotomous data relating to new-onset diabetes were extracted, according to the definitions used in the included studies, in order to calculate the relative risks (RRs). Mean values with standard deviations or median values and percentage change were extracted for continuous outcomes to obtain the percentage change in mean group values from baseline to follow-up, ultimately to calculate the net treatment effect.
Methods of synthesis
The RRs were pooled using a random-effects model. Continuous variables were pooled using the weighted mean difference (WMD), with 95% confidence intervals (CIs).

Heterogeneity was assessed using the $\chi^2$ test. Subgroup analyses were conducted by type of agent (oral or transdermal) and dose, and analyses were compared with each other using a test for interaction. Further analyses were undertaken for type of oral agent (oral conjugated or oral esterified oestrogens), where appropriate. Sensitivity analyses were also conducted to evaluate the effect of study quality and the effect of studies reporting median values for outcomes.

Results of the review
One hundred and seven RCTs (n=33,315) were included in the review. The mean sample size was 311 patients and the mean drop-out rate was approximately 9.2% in the intervention group and 7.2% in the control group.

The authors reported that funnel plots showed no evidence of bias, but data were not presented in the review. There were some discrepancies between the numbers reported in the text and those in the tables; numbers from the text have been used in this abstract.

Abdominal obesity (9 studies): HRT was reported to be more beneficial in non-diabetic women compared with controls, increasing lean body mass (WMD 3.3%, 95% CI: 0.02, 6.6). Pooled results for 5 studies showed reduced waist circumference in the intervention group (WMD -0.8%, 95% CI: -1.2, -0.4, p<0.05), and 4 studies showed reductions in abdominal fat (WMD -6.8%, 95% CI: -11.8, -1.9).

Insulin resistance and diabetes (18 studies): insulin resistance (homeostasis model assessment, HOMA-IR) was significantly reduced in non-diabetic women receiving HRT compared with controls (WMD 12.9%, 95% CI: 8.6, 17.1, p<0.05). Significant differences were reported for fasting glucose and fasting insulin, also favouring HRT (respectively: WMD 2.5%, 95% CI: 1.5, 3.5; WMD 9.3%, 95% CI: 4.9, 13.7). The RR for developing diabetes mellitus indicated a 30% reduction in new-onset diabetes in those receiving HRT (RR 0.7, 95% CI: 0.6, 0.9). Subgroup analyses by agent type showed no significant differences in HOMA-IR. HRT reduced HOMA-IR, fasting glucose and fasting insulin in women with diabetes compared with controls (respectively: WMD 35.8, 95% CI: 19.8, 51.7; WMD 11.5, 95% CI: 5.1, 18.0; WMD 20.2%, 95% CI: 4.2, 36.3). A greater reduction in HOMA-IR was observed for women with diabetes compared with non-diabetics (p=0.07).

Lipids and lipoproteins (61 studies): HRT increased high-density lipoprotein (HDL) cholesterol and decreased low-density lipoprotein (LDL) cholesterol, LDL/HDL ratio (WMD -15.7%, 95% CI: -18.0, -13.5, p<0.05) and lipoprotein(a) (WMD -25%, 95% CI: -32.9, -17.1, p<0.05) compared with controls. Subgroup analyses indicated greater reductions in the LDL/HDL ratio using oral agents compared with transdermal agents (p=0.004), and conjugated oestrogens compared with oral esterified oestrogens (p<0.0001). A significant dose-dependent effect for conjugated oestrogens was reported for LDL/HDL ratio (p=0.0001). Fifty-four studies reported no significant effect of HRT on triglycerides. Subgroup analyses indicated increased levels of triglycerides with oral agents (WMD 6.0%, 95% CI: 4.3, 7.6, p<0.05).

Mean blood-pressure: HRT significantly reduced blood-pressure (WMD -1.7%, 95% CI: -2.9, -0.5, p<0.05). Subgroup analyses indicated a significant reduction using conjugated oestrogens only.

Inflammatory components (15 studies): HRT significantly increased C-reactive protein, thus favouring controls (WMD 37%, 95% CI: 17.4, 61.3, p<0.05). However, significant differences were reported between the intervention and control groups for E-selectin reduction, in favour of HRT (WMD -17.3%, 95% CI: -22.4, -12.1, p<0.05). Subgroup analyses did not significantly alter these results. Subgroup analyses for C-reactive protein indicated a significant increase using oral agents (WMD 47.0%, 95% CI: 29.0, 67.0, p<0.05). Single oestrogens showed greater increases in C-reactive protein compared with combined treatment, and there was a significant dose-dependent effect (p=0.0006).

Thrombotic components (40 studies): HRT significantly reduced fibrinogen (24 studies; WMD -5.5%, 95% CI: -7.8, -3.2, p<0.05) and plasminogen activator inhibitor-1 (16 studies; WMD -25.1%, 95% CI: -33.6, -15.5) . Subgroup analyses did not significantly alter the results for fibrinogen, but indicated a significant reduction in plasminogen activator inhibitor-1 using oral agents (WMD -27.0%, 95% CI: -38.0, -22.0). There were no significant differences for
protein C or protein S by treatment type. Subgroup analyses indicated a significant reduction in protein S using oral agents (WMD 8.6%, 95% CI: -13.1, -4.1, p<0.05).

Sensitivity analyses did not significantly alter the results. Interactions between subgroups were reported in the review and analyses of other outcomes were discussed.

Significant heterogeneity was reported for LDL/HDL ratio, triglycerides, blood-pressure, C-reactive protein, protein S and plasminogen activator inhibitor-1.

**Authors’ conclusions**

HRT reduced abdominal obesity, insulin resistance, new-onset diabetes, lipids, blood-pressure, adhesion molecules and procoagulant factors in women without diabetes, and reduced insulin resistance and fasting glucose in women with diabetes. Oral agents adversely affected C-reactive protein and protein S, while transdermal agents had no effect.

**CRD commentary**

The review question was clear and was supported by appropriate inclusion criteria for the participants, intervention, outcomes and study design. Relevant literature searches of publications in any language were conducted using several electronic databases. However, no other sources were searched and, as there was no apparent attempt to search for unpublished material, it is possible that relevant papers were missed. There were no details of the methods undertaken for the study selection and validity assessment processes, thus the potential for reviewer error and bias cannot be ruled out. The validity of the studies was assessed using appropriate criteria and the results utilised in the synthesis. However, the results of the validity assessment were not reported, thereby limiting our interpretation of the findings. Significant heterogeneity was reported for certain studies and the authors also highlighted methodological differences; the authors made attempts to investigate possible reasons for these differences using sensitivity analyses. Although it is understandable that details of the individual studies were not included in the review because of the large number of included studies, the absence of such details makes it difficult to determine how relevant the studies were to the review question. A number of limitations, such as uncertain quality of the included studies, the presence of heterogeneity and lack of reporting of review methodology, limit any robust conclusions.

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

The authors did not state any implications for practice or further research.

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