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Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials

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Abstract

Background: Hormone replacement therapy (HRT) is often seen as the treatment of choice for preventing fractures in women. We undertook a recent meta-analysis of randomised trials which suggested that HRT reduced non-vertebral fractures by 30%. In this analysis we extend that analysis to vertebral fractures.

Methods: We searched the main electronic databases until the end of August 2001. We sought all randomised controlled trials (RCTs) of HRT where women had been randomised to at least 12 months of HRT or to no HRT.

Results: We found 13 RCTs. Overall there was a 33% reduction in vertebral fractures (95% confidence interval (CI) 45% to 98%).

Conclusions: This review and meta-analysis showed a significant reduction in vertebral fractures associated with HRT use.

Background

Hormone replacement therapy (HRT) is often considered to reduce vertebral fractures by about 60% [1]. This view is based upon the results of one trial, which counted the number of fractures rather than the number of women with fractures. If an analysis is undertaken looking at the number of women with an incident vertebral fracture the reduction is less and is not statistically significant [2]. We have recently reported in a systematic review of 22 randomised-controlled trials that hormone replacement therapy (HRT) reduces non-vertebral fractures by about 30% [3]. To see if there were a similar effect on vertebral fractures we have extended our review to include such fractures.

Methods

Our search strategy has been previously reported; [3] however, in brief, we searched all the main electronic databases for any RCT of HRT and contacted investigators for unpublished data. There were no language restrictions. To be included in the review trials had to be longer than 12 months and include a comparator group who were either taking an inactive placebo, calcium with or without vitamin D, or using no treatment. Up until the end of August 2001, after excluding duplicate reports, we identified 72 potentially relevant trials.

Results

We identified 13 eligible studies. Nine of which came from our original review of 22 trials [4–12]. The four additional trials, not previously included, were identified as...
follows. Two trials were excluded from our previous review as they only reported vertebral fractures [1,13] and are now included and two further studies were identified in a recent update of our search [14,15]. We combined the trials in a meta-analysis using a random effects model.

We assessed 12 studies for quality, the remaining study being available in abstract form only [15]. Trial quality was generally good. All studies were reported as randomised controlled trials with seven reporting the method of randomisation used. In addition nine trials were double blind by design and almost all trials reported on drop-outs or withdrawals and document the reasons for these events.

The table shows the characteristics of the included trials. Eight [1,7,10–15] of the 13 studies assessed fracture incidence using radiographs whilst the remaining five appeared to report only symptomatic fractures.

Figure 1 shows the number of women in each treatment group and their relative risk of fracture. As the figure shows there was an approximate 33% reduction in vertebral fractures among women randomised to HRT (p = 0.04). Three of the studies were undertaken among women who had established osteoporosis [1,11,15]. The relative risk of fracture among these women was 0.47 (95% CI 0.25 to 0.89, p = 0.02), whilst the relative risk of the 10 trials among women without osteoporosis was 0.81 (95% CI 0.50 to 1.33, p = 0.40). Five trials were undertaken among women with a mean age of less than 60 years [5,7–9,13]: the pooled relative risk of fracture for these women was 0.61 (95% CI 0.16 to 2.36), whilst for women older than 60 years it was 0.63 (95%CI 0.41 to 0.96).

**Discussion**

This review of the effects of HRT on vertebral fractures showed a similar reduction in events as did our previous analysis on non-vertebral fractures. As in our previous review the quality of the trials was generally good [3]. Our previous review noted a decreasing effect of HRT on non vertebral fractures for women starting therapy when older than 60 years [3]. In this study we did not observe a similar relationship. Although the relative risk of frac-

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**Table 1: Description of HRT Trials.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Length months</th>
<th>Type of Oestrogen</th>
<th>Progestin+ Addition of calcium*</th>
<th>Study Population</th>
<th>Outcome measure</th>
<th>Age (SD/range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alexander 1999</td>
<td>22</td>
<td>50-ug transdermal estradiol</td>
<td>+</td>
<td>Healthy postmenopausal women with low BMD</td>
<td>BMD</td>
<td>65 (2.2)</td>
</tr>
<tr>
<td>Delmas 2000</td>
<td>24</td>
<td>Oral 1 mg estradiol</td>
<td>+</td>
<td>Healthy &gt;1 year postmenopausal women with normal BMD</td>
<td>BMD</td>
<td>58 (5)</td>
</tr>
<tr>
<td>Gallagher 2001</td>
<td>36</td>
<td>Oral 0.625 mg conjugated estrogens</td>
<td>+</td>
<td>Elderly women with normal bone density</td>
<td>BMD</td>
<td>72(± 4)</td>
</tr>
<tr>
<td>Cauley 2001</td>
<td>49</td>
<td>Oral 0.625 conjugated estrogen</td>
<td>+</td>
<td>Women with established coronary disease &gt;5 years post menopause</td>
<td>MI or CHD</td>
<td>67</td>
</tr>
<tr>
<td>Herrington 2000</td>
<td>38</td>
<td>Oral 0.625 conjugated estrogen</td>
<td>+</td>
<td>Women with coronary arterial disease (CAD)</td>
<td>BMD</td>
<td>66 (7.0)</td>
</tr>
<tr>
<td>Ishids 2001</td>
<td>12</td>
<td>Oral 0.625 conjugated estrogen</td>
<td>+</td>
<td>Women with established osteoporosis</td>
<td>BMD</td>
<td>70 (7.6)</td>
</tr>
<tr>
<td>Lindsay 1990</td>
<td>24</td>
<td>Oral 0.625 mg conjugated estrogen</td>
<td>+</td>
<td>Postmenopausal women with 1+ vertebral fracture &amp; low BMD</td>
<td>BMD</td>
<td>48 (1.0)</td>
</tr>
<tr>
<td>Lufkin 1992</td>
<td>12</td>
<td>Transdermal 0.1 mg 17β-estradiol</td>
<td>+</td>
<td>Postmenopausal white women with documented osteoporosis</td>
<td>BMD</td>
<td>64.8 (54.9 to 71.3)</td>
</tr>
<tr>
<td>Mosekilde 2000</td>
<td>60</td>
<td>Oral 1 mg or 2 mg estradiol</td>
<td>+</td>
<td>Healthy women 3–24 months post menopause</td>
<td>Fractures</td>
<td>50 (2.8)</td>
</tr>
<tr>
<td>PEPI 1996</td>
<td>36</td>
<td>Oral 0.625 mg conjugated estrogen</td>
<td>+</td>
<td>Healthy women 1–10 years post menopause normal BMD</td>
<td>BMD</td>
<td>56 (0.3)</td>
</tr>
<tr>
<td>Ravn 1999</td>
<td>48</td>
<td>Oral 0.625 conjugated estrogen or 2 mg estradiol</td>
<td>+</td>
<td>Healthy 6+ months postmenopausal women under 60 years</td>
<td>BMD</td>
<td>55</td>
</tr>
<tr>
<td>Recker 1999</td>
<td>42</td>
<td>0.3 mg conjugated estrogen</td>
<td>+</td>
<td>Healthy women average BMD t-score-3.5 at femur</td>
<td>BMD</td>
<td>73 (5.0)</td>
</tr>
<tr>
<td>Wimalawansa 1998</td>
<td>48</td>
<td>Oral 0.625 conjugated estrogen</td>
<td>+</td>
<td>Women with established osteoporosis (1+vertebral fracture)</td>
<td>BMD</td>
<td>65 (0.9)</td>
</tr>
</tbody>
</table>
tution, any comments, or any other reference not directly cited in the text. This review was partly funded from an unrestricted educational grant from Wyeth Pharmaceuticals. We thank Cynthia Iglesias and Andrea Manca for screening Spanish and Italian language papers for us.

**References**


**Figure 1**

Forest plot of randomised trials of HRT and vertebral fracture incidence.


15. Ishida Y, Soh H, Tsuchida M, Kawahara S, Murata H: Comparison of the Effectiveness of Hormone Replacement Therapy, Bisphosphonate, Calcitonin, Vitamin D and Vitamin K in Postmenopausal Osteoporosis: A One Year Prospective Randomized Controlled Trial. Bone 2001, 28 Supp 1:S224
