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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.
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-

**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>Alexandersen 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 [5]</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 [14]</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 [4]</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 Progression</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 artery disease (CAD)</td>
<td>BMD</td>
<td>66 (7.0)</td>
</tr>
<tr>
<td>Ishida 2001 [15]</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 [13]</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 [1]</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 [7]</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 [8]</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 [9]</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 [10]</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>
ture reduction for younger women was not statistically
significant it was virtually identical to that for older
women (i.e RR = 0.61 and 0.63 for younger and older
women respectively). There were fewer events and fewer
participants in trials among women with a mean age of
less than 60 years and this may explain the lack of statis-
tical significance.

Studies of other anti-fracture drugs, such as the bisphos-
phonates, have suggested an enhanced effect among pa-
tients with established osteoporosis [16]. This review
may support an interaction between HRT and the pres-
ence of osteoporosis on vertebral fracture incidence, al-
though the number of trials in that sub-group are small,
so definitive conclusions cannot be drawn on this issue.
This may be a chance finding, however, because our pre-
vious review, where nearly all included women were not
osteoporotic, showed an HRT effect on non-vertebral
fractures [3]. With respect to the effects, or otherwise, of
HRT among women who have low bone density without
a prior vertebral fracture there were no studies that al-
lowed us to explore HRT's effects on this sub-group.

Interestingly, taking the results of this review along with
our previous analysis shows a similar effect on fractures
as the large RCT of the Selective Estrogen Receptor Mod-
ulator (SERM) raloxifene [17]. In that trial, among wom-
en with a mean age of 67 years, a 50% reduction in new
vertebral fractures was observed among osteoporotic
women whilst a small, non-significant reduction in non-
vertebral fractures was observed [17]. The issue as to
whether HRT does significantly reduce vertebral and
other fractures needs to be tested in large randomised
trials with fracture as an endpoint. Fortunately, ongoing
trials of HRT are large enough to answer this important
question.

**Conclusion**

In summary, our review has shown that HRT use is asso-
ciated with reduction in vertebral fractures, particularly
among osteoporotic women.

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