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Estrogen treatment does not reduce fractures?

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The title may come as a shock to many of those who take the fracture effect of estrogens as a matter of faith, considering all of the studies in the literature. However, a recent article from the Women's Health Initiative (WHI) in this issue of *Menopause* suggests that this belief might be more faith than science. The results in this issue of *Menopause* suggest that estrogen only reduces fractures when combined with calcium.¹

The rationale for using estrogen to prevent fractures is strongly founded on the pathophysiology of bone loss. Rapid bone loss occurs in all skeletal sites after menopause, and the average cumulative loss in bone mineral density (BMD) from 1 year premenopause to 3 years postmenopause is about 9% to 10% in both spine and hip, which is equivalent to a *T* score of about 0.7. One can actually estimate that more than 30% of women lose more than 1 *T* score.²

Menopausal bone loss can be completely prevented by estrogen, and numerous studies have shown that both oral and transdermal estrogen are very effective in preventing both postmenopausal and age-related bone loss. In the largest individual trial of postmenopausal women (N = 822) from the Health, Osteoporosis, Progestin, Estrogen (HOPE) trial, which evaluated three doses of estrogen, even small doses of estrogen were effective in preventing bone loss.³

A large number of studies in the literature showed a beneficial effect of estrogen in reducing fractures, and this was supported by cohort fracture data. In a meta-analysis of 21 studies, estrogen was shown to reduce nonvertebral fractures by 27% (relative risk [RR], 0.73; 95% CI, 0.56-0.94); however, when divided by age (<60 y or ≥60 y), the effect was not significant in the older age group (RR, 0.88; 95% CI, 0.71-1.08).⁴ In another meta-analysis of 13 studies, there was a significant reduction (33%) of vertebral fractures with estrogen treatment (RR, 0.33; 95% CI, 0.15-0.73).⁵

Once estrogen is discontinued, rapid bone loss occurs.^{6,7} In these studies, the decrease in BMD in 1 year was 5% to 6%, similar to the rapid menopausal bone loss described earlier in the Study of Women's Health Across the Nation.² This is worrying because it means that estrogen discontinuation has an important adverse effect particularly when BMD is low (*T* score, -1.5 to -1.8).

Could estrogen discontinuation increase fracture risk? There is evidence for this hypothesis. In the Million Women Study in England, current users of hormones had a significant 38% reduction in fractures; among those who discontinued hormones, the fracture rate was similar to that in the untreated population within 1 year.⁸ In a study of a large managed care group in California, the number of women taking estrogen declined from 85% to 18% between 2002 and 2007, and follow-up of this group for 6 years showed a significant 50% increase in hip fractures by the end of the second year off estrogen.⁹

Given that background, the results from this article in this issue of *Menopause* are perhaps less surprising. This article by Robbins et al¹ published, for the first time, fracture data from the partial factorial study in the WHI. Briefly, the study design was as follows: women were initially randomized to either hormone therapy (HT; conjugated estrogens 0.625 mg + medroxyprogesterone acetate 2.5 mg), estrogen therapy (ET; conjugated estrogens 0.625 mg), or placebo. In the second or third year, they were invited to join the calcium and vitamin D (CaD) trial and were randomized to calcium 1,000 mg and vitamin D 400 IU (CaD) or placebo. This was the basis of the partial factorial study.

The numbers are instructive: women aged between 50 and 79 years were randomized to HT/ET (27,347), HT or placebo (16,608), and ET/placebo (10,739). During the second year and third year, 16,089 women from the HT/ET arms entered the CaD study. Also, 20,193 women from the dietary modification study entered the CaD trial but were not part of the HT/ET trial.

After randomization had been completed in the partial factorial study, there were 18,176 women in the active CaD arm: 4,039 women on active HT/ET; 4,015 women on placebo HT/ET; and 10,122 women on CaD only. In the placebo CaD arm, there were 18,106 women: 4,078 on active HT/ET; 3,957 on placebo HT/ET; and 10,071 on placebo CaD only. This means that approximately 20% of the CaD arms were also on active HT/ET. These should be significant group sizes for examining the interaction between HT/ET and CaD on hip fractures (primary outcome).

There are three main findings from the analysis of the factorial study. CaD does not reduce hip fractures (hazard ratio [HR], 1.20; 95% CI, 0.85-1.69) and HT/ET alone does not reduce hip fractures (HR, 0.87; 95% CI, 0.60-1.26), but the combination of active HT/ET and active CaD significantly reduces hip fractures (HR, 0.43; 95% CI, 0.28-0.60).

In an extended statistical analysis, they showed that as total intake (supplement + diet) of calcium and vitamin D increased to 3,000 mg and 1,200 IU, respectively, there was further reduction in fractures.

BMD data in this partial factorial study did not show a synergistic effect between HT/ET and calcium; this may have been caused by much lower numbers in the BMD subgroups compared with the fracture study. A previous review of the literature comparing changes in BMD between 20 studies on estrogen plus calcium and 11 studies on estrogen alone showed that the increase in BMD was 2% higher at the spine and femoral neck with the combination.¹⁰

These results raise questions about the previously reported fracture results from the WHI studies.^{11,13} The original fracture articles on HT/ET actually included CaD in a significant number of women, and these data should be reanalyzed excluding those who were in the CaD factorial study to see if HT/ET indeed does not reduce fractures.^{11,12} Another puzzling point in this article is the absence of synergistic effect between HT/ET and CaD on other osteoporotic fractures, because earlier WHI articles showed that HT/ET reduced all types of fractures.^{11,12}

The previous WHI fracture study with CaD should also be reexamined.¹³ In the intention-to-treat analysis, CaD had no effect on fractures; however, a subgroup analysis of the adherence group showed a significant 30% reduction in hip fractures with CaD. Is it possible that the fracture reduction was attributable to the subgroup that was also on HT/ET?

A possible concern with this analysis is that HT ended in July 2002 but hip fracture data were collected 3 years later in March 2005. The ET study ended in February 2004—1 year before final fracture data collection. For the HT group, this 3-year gap may be significant. For instance, in the study from the managed care group, the incidence of hip fractures increased by 52% (RR, 1.52; 95% CI, 1.26-1.84) on the second year after HT/ET discontinuation⁹; in another large study in the UK, the incident fracture rate for current HT/ET users was 0.62 (95% CI, 0.58-0.66) compared with 1.09 (95% CI, 0.91-1.30) in the first year off hormones.⁸ Yet another explanation is that the significant effect in this study is attributable to chance despite the low *P* value.

What is the possible mechanism for this synergistic effect? It is known that estrogen has a much more potent antiresorptive effect on bone than calcium. One explanation is that combining both treatments yields a greater effect because each has a different action at some stage in the bone remodeling cycle.

In summary, this factorial study from the WHI shows no significant effect of HT/ET or calcium on fractures when given separately, but a significant reduction in fractures when given together. However, further analysis of previous fracture studies in the WHI is now needed to see whether HT/ET has indeed “no effect” on fractures.

How much CaD should be combined with HT/ET? There was a significant increase in kidney stones in the WHI CaD study, and the average total daily intake of calcium and vitamin D was 2,150 mg and 770 IU, respectively.¹³ Excess calcium supplementation was, most probably, the cause of the increase in kidney stones because vitamin D at daily doses below 4,000 IU has a very minor effect on calcium absorption.¹⁴ This article shows that total daily calcium and vitamin D intake of 1,200 mg and 600 to 800 IU, given together with HT, is sufficient to reduce fractures.

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