

Bone-Related Effects of Low-Dose HRT

Recker RR, Davies KM, Dowd RM, Heaney RP. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. *Ann Intern Med* 1999;130:897-904.

Study Overview

Objective. To determine the bone-sparing effect and tolerability of continuous low-dose hormone replacement therapy (HRT) in elderly women.

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. Academic osteoporosis research and clinical center. A convenience sample of 128 healthy white women older than 65 years with low bone mass who met various exclusion criteria. The primary eligibility criterion was low bone mass, defined as spinal bone mineral density of 0.90 g/cm² or less (T score \leq -1.336) as measured by dual-energy x-ray absorptiometry.

Methods. Participants were randomized to receive either low-dose HRT therapy ($n = 64$) or matching placebo ($n = 64$) continuously over 3.5 years. Low-dose HRT therapy consisted of conjugated equine estrogen (0.3 mg/day) and medroxyprogesterone (2.5 mg/day). Both groups received calcium and vitamin D supplementation to maintain calcium intake above 1 g/day and serum 25-hydroxyvitamin D levels of at least 75 nmol/L.

Main outcome measures. Bone mineral density of the spine, hip, total body, and forearm; serum total alkaline phosphatase and serum osteocalcin levels at 6-month intervals; and 24-hour urine creatinine and hydroxyproline excretion at baseline, 12 months, and 42 months.

Main results. Eighteen patients (28%) in the HRT group and 12 patients (19%) in the placebo group stopped therapy. Adherence among those who remained was estimated to range between 90% and 96% over the entire course of the study, as revealed by pill count. During 3.5 years of observation of the HRT group, spinal bone mineral density increased by 3.5% ($P \leq 0.001$) in an intention-to-treat analysis and by 5.2% among patients with greater than 90% adher-

ence to therapy. Significant increases were seen in total-body and forearm bone density ($P < 0.001$). No significant losses occurred at the spine or total body in patients who received placebo plus vitamin D and calcium supplementation.

Symptoms related to HRT (breast tenderness, spotting, pelvic discomfort, and mood changes) were mild, and most disappeared within 6 months. Only 11% of patients in the HRT group and 6% of patients in the placebo group had symptoms of more than 12 months' duration. No patients had vaginal spotting or bleeding beyond 12 months, and no thromboembolic episodes occurred.

Conclusion

Continuous low-dose HRT with conjugated equine estrogen and oral medroxyprogesterone combined with adequate calcium and vitamin D intake provides a bone-sparing effect similar or superior to that provided by other, higher-dose HRT regimens in elderly women and is well tolerated by many patients.

Commentary

The bone-sparing effects and tolerability reported by Recker and colleagues are the most positive for low-dose HRT to date. These findings suggest the value of using a low-dose regimen, but they need to be replicated in larger sample sizes with longer follow-up and more definitive clinical endpoints. This study used a convenience sample of white women, which is not representative of the population that could receive HRT or benefit from it. Furthermore, the endpoint for efficacy was a laboratory measurement of bone density. With longer follow-up, critical clinical outcomes (eg, fracture) or potentially severe side effects (eg, endometrial carcinoma) could be assessed.

Applications for Clinical Practice

Because of the severe, dose-related side effects associated with long-term HRT, only about 20% of women who could benefit from HRT are taking it, and only two thirds of

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prescriptions are actually filled [1,2]. Previous studies did not show benefits of low-dose, long-term HRT in elderly women, perhaps because of inadequate calcium and vitamin D intake in the subjects, small sample size, and excessive study drop out. The lowest daily dose thought to produce positive bone effects was 0.625 mg of conjugated equine estrogens or its equivalent [3,4]. This study illustrates that most women can receive the benefits of long-term HRT with less than half that dosage, as long as they receive adequate calcium and vitamin D supplementation. However, as noted above, a number of issues must be resolved before this type of therapy can be more widely recommended.

References

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4. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. The Writing Group for the PEPI. *JAMA* 1996; 276:1389-96.

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