Endocrine, vol. 6, no. 2, 207–211, April 1997 0969-711X/97/6:207-211/$9.25

Use of Estrogen for Prevention and Treatment of Osteoporosis

Robert Marcus

Aging Study Unit, Geriatrics Research, Education & Clinical Center, VA Medical Center Palo Alto, and the Department of Medicine, Stanford University, Stanford, CA

Introduction

Two decades of experience leaves no doubt that sustained administration of estrogen to menopausal women conserves bone throughout the skeleton and offers protection against fracture. On the other hand, uncertainty remains about many aspects of this issue. These include the optimal type, dose, and mode of administration of estrogen; about the proper selection of women to offer estrogen, the age at which treatment should be initiated, and its duration; and about the consequence of adding progestins to the treatment regimen. Reviewed here is current evidence regarding selected aspects of the skeletal effects of hormone replacement therapy. These include the magnitude of expected gains in bone mineral density (BMD) in response to estrogen, the skeletal impact of adding progestin on this response, the expected failure rate when women are treated with estrogen, the need for prolonged continuation of estrogen in order to appreciate its antifracture benefits, and the development of "designer" estrogens to obviate undesirable consequences of estrogen on the uterus and breast.

Menopausal Changes in Skeletal Homeostasis

Peak bone mass remains relatively stable from about age 25 yr until about age 50, although earlier bone loss from the hip may occur. Evidence suggests that menopausal acceleration of bone loss begins when circulating estradiol concentrations decrease. Menopausal loss affects the entire skeleton, but is particularly marked in trabecular bone, reflecting its higher prevalence of bone surfaces, where turnover occurs. The magnitude of estrogen-related bone loss represents a two- to threefold increase in turnover rate, and results 5 yr later in a typical decrease in BMD of about 15%, or about one standard deviation.

Several years following last menses, bone turnover decreases. Cross-sectional studies indicate that the annual decrease in BMD slows and even stabilizes after about age 70 yr, but some recent studies indicate persistence of increased bone turnover in estrogen-deplete women well into the eighth decade *(1,2)*. Body weight has a major influence on postmenopausal bone loss, heavier subjects being relatively protected *(3)*, perhaps related to their higher degree of mechanical loading, or to their higher circulating concentrations of estrone.

Considerable attention has been given to identifying women at menopause who are likely to be "fast losers," and, therefore, most likely to benefit from hormonal intervention. It remains uncertain whether such a discrete subgroup actually exists, or whether rates of bone loss at menopause are normally distributed.

Skeletal Effects of Estrogen Replacement Therapy

Conjugated estrogens were approved for marketing in the United States in 1942. This product was approved initially because it had satisfied a requirement to be shown safe for its intended use in the treatment of menopausal symptoms, vaginitis, and amenorrhea. Following 1962, when it became necessary to show efficacy as well as safety, the Food and Drug Administration (FDA) announced a group of estrogen products to have satisfied this additional requirement for their original intentions, and to be "probably effective" for selected cases of osteoporosis. In 1986, the FDA upgraded the status of estrogen to "effective" for use in postmenopausal osteoporosis. At present, the following preparations and daily doses have been approved for osteoporosis: Conjugated equine estrogens, 0.625 mg (Premarin®), 17β-estradiol transdermal patches, 0.05 mg (Estraderm®), and Piperazine estrone sulfate tablets 0.75 mg (Ogen®).

It is axiomatic that initiation of estrogen replacement at the time of oophorectomy or within the first few years after natural menopause conserves bone mass. In 1976, Lindsay et al. *(4)* reported a clinical trial in which oophorectomized women had been randomly assigned to receive mestranol, average dose 24 μg/d, or placebo. The placebo group progressively lost metacarpal bone, but bone mineral was maintained in the treatment group, a finding that persisted for 10 yr of followup *(5)* (Fig. 1). Similar results were achieved subsequently with other estrogen preparations, with other measurement techniques, and at multiple skeletal sites *(5,6–9)*. As a means to protect bone mass in the early menopausal years, estrogen is significantly more

Received December 20, 1996; Accepted January 13, 1997.
Author to whom correspondence and reprint requests should be addressed: Dr. R. Marcus, Aging Study Unit, Geriatrics Research, VA Medical Center, Palo Alto, CA 94304.

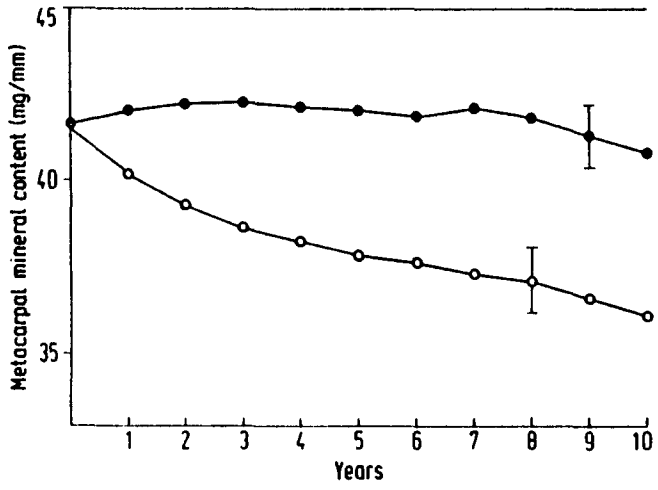

Fig. 1. Effect of estrogen on metacarpal bone mineral content. Filled circles represent estrogen treated women; open circles represent placebo treatment. Reproduced from Lindsay et al. *(5)* with permission.

effective than calcium, vitamin D and its metabolites, and thiazide diuretics.

The curvilinear nature of menopausal bone loss engendered the idea that once the accelerated phase of early menopause subsides there is little to be gained by starting estrogen. Strong evidence argues against this view and for the conclusion that estrogen protects bone mass even if started well beyond the initial menopausal years *(7,10,11)*. However, there presently is insufficient information regarding fracture outcomes in women who start estrogen at an advanced age.

The changes in BMD that are observed when women who are more than 5 yr beyond last menses generally follow a pattern that is predictable from an understanding of the hormone's role as an antiresorptive agent: BMD rises over 12 to 18 mo, followed by a plateau. This pattern is most compatible with an estrogen-induced decrease in the "remodeling space," a transient deficit in bone that represents areas where resorption has taken place, but where the formation response has not yet started or remains in progress. The plateau indicates restoration of this remodeling transient to a new steady-state level.

In the recently concluded 3-yr multicenter postmenopausal estrogen/progestin interventions trial (PEPI) *(12,13)*, the effects of estrogen, with and without added progestin, were assessed on BMD of the spine and hip. Over 3 yr of active therapy, unopposed estrogen increased BMD in a curvilinear pattern, resulting in a 5% increase at the lumbar spine and a 2% increase at the proximal femur. Women receiving the same dose of estrogen plus cyclic medroxyprogesterone (MPA) (10 mg/d for 12 d each month), continuous 2.5 mg/d MPA, or cyclic micronized progesterone (200 mg/d for 12 d each month) showed the same rise in BMD at both the spine and hip that was seen with unopposed estrogen *(13)*.

For women with an intact uterus, either cyclic or continuous administration of a progestin is considered the standard of care for protection against endometrial hyperplasia and cancer, but little information has been available to predict the skeletal consequences of combination therapy. It is reassuring to note that addition of a progestin to estrogen was a neutral event for the skeleton in the PEPI cohort. It should be remembered that increases in BMD have been reported for norethindrone, but this likely reflects the fact that this progestin (as well as all 19-nor testosterone-related progestins) has intrinsic androgenic activity that is not shared by natural progesterone or MPA.

Estrogen Dose

Before discussing what is known about the estrogen dose required for skeletal protection, the inadequacies of knowledge in this field must be acknowledged. Studies directly addressing this issue are few in number and generally involve very few patients. In one of the primary reports on which FDA approval of estrogen was based, only six women were assigned the 0.6 mg hormone dose at which BMD maintenance was observed *(6)*. Moreover, studies have generally been conducted to assess the dose of hormone necessary for a treatment group to show BMD conservation relative to a placebo group. They have rarely had adequate power to compare one dose of hormone with another, and do not delineate the response rate of individual. If dosing studies are to be an aid to effective therapy, one must know how many patients can be expected to respond (or *not* to respond) to any given dose. Finally, with few exceptions, conclusions regarding minimum effective dose reflect the experience at only one skeletal site, usually the spine.

That being said, a few generalizations can be offered. Doses of estrogen sufficient to elevate plasma 17β-estradiol concentrations to about 70 pg/mL suppress bone remodeling and protect bone mass at the spine. Ettinger et al. *(14)* conducted a dose-response test of micronized 17β-estradiol in women who had been menopausal for up to 5 yr. Women receiving 0.5, 1.0, and 2.0 mg of drug showed annual increases in lumbar spine BMD of 0.3, 1.8, and 2.5%, respectively, but even at "effective doses," a substantial number of women were observed to have lost bone.

For conjugated equine estrogens, 0.625 mg/d has been considered sufficient. In one report, spine BMD was protected by as little as 0.3 mg of conjugated estrogens if patients also received supplemental calcium *(15)*. However, not all skeletal regions respond with identical sensitivity to estrogen, and the adequacy of the latter approach for conserving hip BMD has not been established. Differential sensitivity may also affect the response to different estrogens, particularly those with intrinsically lower potency, such as estrone or estriol. For example, 2 yr treatment with 0.625 mg/d of estrone sulfate conferred protection at the spine, but 1.25 mg was necessary to protect the proximal femur *(16)*.

Data from PEPI give insight to the number of women who do not conserve bone when treated with 0.625 mg/d conjugated estrogens. Since the precision error of BMD estimates in PEPI was 1.5%, one can be confident that an apparent change in BMD over time would be real if it exceeded about 4%. In the placebo group, about 50% of women showed at least that much bone loss from the lumbar spine over 3 yr. For women in active treatment groups who took at least 80% of their assigned study medication, fewer than 5% lost 4% from the spine, and about 6% lost that much from the femoral neck over 3 yr. Thus, physicians can be reassured that if patients take their medication, the standard 0.625 mg dose of conjugated estrogen offers substantial skeletal protection at both the spine and hip.

Route of Administration

The route of estrogen delivery appears not to be critical for skeletal response, since transdermal 17β-estradiol influences bone turnover and bone mass similarly to oral hormone *(17)*. Published data suggest that the minimum dose for spine BMD preservation by transdermal estradiol is given with the 50 μg patch.

Estrogen and Fracture

Data suggesting that estrogen protects against fragility-related fractures are relatively sparse compared to those showing effects on bone mass. In an early clinical trial, Nachtigall et al. *(18)* showed less vertebral deformity in women assigned to take conjugated equine estrogens than in placebo-treated women. This study was remarkable for two features: it was extremely small in size, and the estrogen dose, 2.5 mg/d of conjugated equine estrogens, was fourfold greater than that typically prescribed for menopausal hormone replacement. That study notwithstanding, most evidence supporting antifracture efficacy of estrogen comes from epidemiologic studies rather than clinical trials. The reason for this, of course, is the nontrivial nature of conducting prospective studies with adequate statistical power. Current industry-sponsored trials aimed at showing antifracture benefit have enrolled several thousand osteoporotic women for at least 3 yr of observation.

Epidemiological studies confirm a lower risk of fracture among women who have taken estrogen *(19–23)* and suggest a magnitude of protection of about 60%. Full realization of this benefit requires sustained hormone administration, probably for 5 yr or more *(21)*. Results from the Framingham study *(22)* indicate that at least 7 yr of estrogen may be needed to achieve protection against fracture, and, in addition, suggest that even this degree of exposure is not adequate to protect bone mass in women beyond 75 yr of age. In contrast, Kanis et al. *(21)* found a 30% reduction in hip fracture risk for estrogen users beyond 80 yr of age. The importance of continuing to take estrogen therapy is seen in the report of Cauley et al. *(23)* from the Study of Osteoporotic Fractures (SOF). After adjusting for many potential confounding factors, current estrogen use was associated with a 34% decreased risk for all nonspinal fractures. Current users who initiated estrogen within 5 yr of last menses had a 50% reduction in risk, but those women who had stopped estrogen experienced no fracture protection, even if they had at one time taken estrogen for more than 10 yr.

It is generally assumed that fracture protection directly reflects preservation of bone mass. Whereas this assumption is certainly compatible with the evidence, additional factors should be considered. In SOF *(23)*, estrogen users showed a reduced risk for all nonspinal fractures even after the data were adjusted for bone mass. Subjects in case-control or observational cohort studies did not randomly decide to take estrogen, and pretreatment characteristics of these women might themselves underlie a lower fracture risk. Women choosing to take estrogen may already exhibit higher than average commitment to healthful behaviors, such as patterns of diet, exercise, and use of alcohol or tobacco, that themselves reduce fracture risk. An important contribution to fracture risk, particularly hip fracture, is the tendency to fall. The great majority of hip fractures occur as the immediate consequence of a fall. The suggestion that long-term estrogen may influence the risk of falls requires investigation.

The favorable and equivalent skeletal response to both oral and other forms of estrogen delivery means for the prescribing physician that choice of estrogen preparation should be based on other considerations. In particular, elevations in high density lipoprotein (HDL) cholesterol and reductions in low density lipoprotein (LDL) cholesterol have been observed primarily with oral estrogen. For women in whom achieving such changes is an important consideration (i.e., in women with higher risk for cardiovascular disease and in whom lipoprotein profiles are unfavorable), an oral estrogen would appear to be a superior choice. On a more practical basis, some women uniquely experience headaches, malaise, or other systemic side-effects with one particular form of estrogen, but can tolerate other preparations. The physician can take comfort in the knowledge that, at least with respect to the skeleton, the method of delivery is not a matter of consequence.

Stopping Estrogen Therapy

Lindsay et al. *(24)* observed an accelerated rate of bone loss in women who abruptly terminated estrogen replacement therapy. In a more complex protocol, Christiansen et al. *(25)* randomly assigned women to estrogen or placebo for 24 mo, at which time the estrogen group either switched to placebo or continued estrogen. The secondary placebo group lost bone over the next 12 mo at the same rate that was observed in subjects who had taken placebo from the beginning (Fig. 2). Thus, the authors found that bone is lost

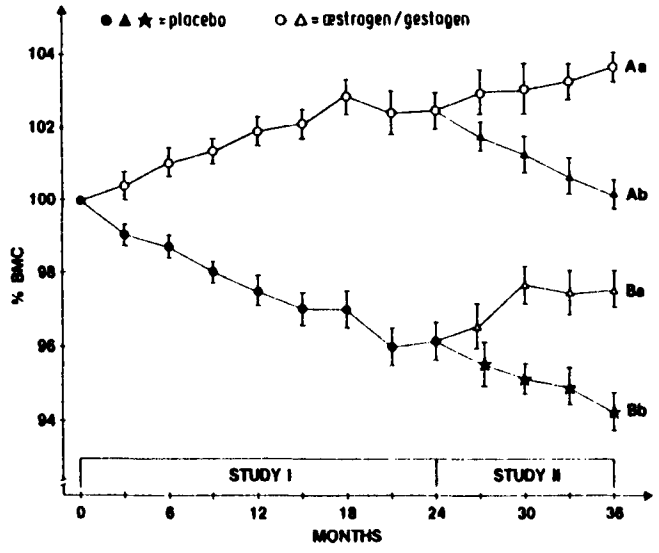

Fig. 2. Effect of estrogen withdrawal on forearm bone mineral content. Subjects were treated initially with either estrogen/progestin (open circles) or placebo (filled circles) for 18 mo. They were then randomly assigned to continue hormone or placebo for an additional 12 mo. Subjects assigned initially to active treatment subsequently lost bone at a rate that was equivalent to that of the original placebo group. Reproduced from Christiansen et al. *(25)* with permission.

beginning (Fig. 2). Thus, the authors found that bone is lost after termination of estrogen, but do not confirm the accelerated rate reported by Lindsay et al. *(24)*.

The Effect of Tamoxifen, an Antiestrogen

One of the most challenging categories of patient to treat is the woman who has recovered or is recovering from breast cancer. Although clinical trials are currently underway to determine whether this policy is wrong, the standard of care in the United States as of 1995 is not to offer estrogen to such women. This is a source of great apprehension on the part of patients, many of them young, who are postmenopausal or who have been rendered postmenopausal by their oncologic management. It appears that tamoxifen, an antiestrogen frequently used as adjuvant therapy for breast cancer, may provide a reasonable solution for many women. Tamoxifen is not a pure estrogen antagonist, but shows partial agonist activity on bone. Several reports indicate that postmenopausal women treated with tamoxifen maintain bone mass *(26–28)*. Additional work with this compound is required, particularly in younger women. It is also important to note that although tamoxifen may act like estrogen in postmenopausal women whose endogenous estrogen concentrations are very low, its use as preventive therapy (e.g., the current National Institutes of Health [NIH] sponsored breast cancer prevention trial) by healthy young women with normal estrogen production may permit its estrogen antagonism to dominate, leading to bone loss.

Conclusions, Concerns, and Future Directions

Despite persistent ambiguity surrounding aspects of this problem, timely and sustained administration of estrogen to menopausal women clearly offers substantial protection against bone loss and fragility fractures. In consideration of evidence that antifracture efficacy is lost for "past users" even if duration of use exceeded 10 yr *(23)*, estrogen replacement should ideally be considered a lifelong strategy for skeletal health. It is a fact of life, however, that women who are initially prescribed estrogen generally take it for only a few months. North American pharmaceutical industry surveys suggest that the "half-life" of estrogen therapy is not much more than 6 mo, a trend that has been stable for the past decade. To some degree, this may reflect the fact that many women are prescribed estrogen for short-term control of vasomotor instability rather than as a long-term health maintenance strategy, but it must also reflect the controversy and public uncertainty that surrounds the entire topic of hormone replacement.

There has never been a time that more than about 30% of the potential estrogen consumers in the United States or other industrialized nations have taken estrogen, and consumption figures are far lower for Asian and third-world countries. Reasons for this are complex, and involve a dislike for taking medication, reluctance to continue vaginal bleeding, and, particularly, concerns about breast cancer. In recognition of these various issues, it is encouraging to note that compounds are under development whose actions mimic those of 17β-estradiol on bone and on lipoproteins, but seem not to lead to potentially adverse effects on the endometrium or the breast. Raloxifene is an example of such an agent. This compound acts either as an estrogen agonist or antagonist, depending on the specific tissue. Administered to oophorectomized rats, raloxifene mimics the skeletal protection actions of 17β-estradiol, but does not stimulate endometrial hyperplasia and antagonizes estrogen action on the breast *(29)*. Clinical trials of raloxifene in postmenopausal osteoporotic women are currently in progress. It is to be hoped that this or similar agents may prove acceptable and effective for many women who are unable or unwilling to take long-term estrogen.

References

1. Blunt, B. A., Klauber, M. R., Barrett-Connor, E. L., and Edelstein, S. L. (1994). *J. Bone Min. Res.* **9**, 1333–1338.
2. Greenspan, S., Maitland, L. A., Myers, E. R., Krasnow, M. B., and Tamiko, H. K. (1994). *J. Bone Min. Res.* **9**, 1959–1965.
3. Harris, S., Dallal, G. E., and Dawson-Hughes, B. (1992). *Calcif. Tissue Int.* **50**, 19–23.
4. Lindsay, R., Hart, D. M., Aitken, J. M., MacDonald, E. B., Anderson, J. B., and Clarke, A. C. (1976). *Lancet* **i**, 1038–1040.
5. Lindsay, R., Hart, D. M., Forrest, C., and Baird, C. (1980). *Lancet* **ii**, 1151–1153.
6. Genant, H. K., Christopher, C. E., Ettinger, B., and Gordan, G. S. (1982). *Ann. Int. Med.* **97**, 699–705.
7. Recker, R. R., Saville, P. D., and Heaney, R. P. (1977). *Ann. Int. Med.* **87**, 649–655.

8. Horsman, A., Gallagher, J. C., Simpson, M., and Nordin, B. E. C. (1977). *Br. Med. J.* **2,** 789–792.
9. Christansen, C., Christensen, M. S., McNair, P., Hagen, C., Stocklund, K., and Transbøl, I. (1980). *Eur. J. Clin. Invest.* **10,** 273–279.
10. Lindsay, R. and Tohme, J. F. (1990). *Obstet. Gynecol.* **76,** 290–295.
11. Quigley, M. E. T., Martin, P. L., Burnier, A. M., and Brooks, P. (1987). *Am. J. Obstet. Gynecol.* **156,** 1516–1523.
12. The PEPI Investigators. (1995). The Postmenopausal Estrogen/Progestins Interventions Trial: rationale, design, and conduct. Controlled Clinical Trials **16,** Supplement 1S–65S.
13. PEPI Trial Investigators Writing Group. (1996). Hormonal effects on bone mineral density in the spine and hip: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* **276,** 1389–1396.
14. Ettinger, B., Genant, H. K., Steiger, P., and Madvig, P. (1992). *Am. J. Obstet. Gynecol.* **166,** 479–488.
15. Ettinger, B., Genant, H. K., and Cann, C. E. (1987). *Ann. Int. Med.* **106,** 40–45.
16. Gallagher, J. C. and Baylink, D. (1990). *J. Bone Miner Res. Suppl.* **2,** 802, Abstract.
17. Stevenson, J. C., Cust, M. P., Gangar, K. F., Hillard, T. C., Lees, B., and Whitehead, M. I. (1990). *Lancet* **ii,** 265–269.
18. Nachtigall, L. E., Nachtigall, R. H., Nachtigall, R. D., and Beckmann, E. M. (1979). *Obstet. Gynecol.* **53,** 277–281.
19. Hutchinson, T. A., Polansky, S. M., and Feinstein, A. R. (1979). *Lancet* **ii,** 705–709.
20. Weiss, N. S., Ure, C. L., Ballard, J. H., Williams, A. R., and Daling, J. R. (1980). *N. Engl. J. Med.* **303,** 1195–1198.
21. Kanis, J. A., Johnell, O., Gullberg, B., Allander, E., Dilsen, G., and Gennari, C. (1992). *Br. Med. J.* **305,** 1124–1128.
22. Felson, D. T., Zhang, Y., Hannon, M. T., Kiel, D. P., Wilson, P. W., and Anderson, J. J. (1993). *N. Engl. J. Med.* **329,** 1141–1146.
23. Cauley, J. A., Seeley, D. G., Enstrud, K., Ettinger, B., Black, D., and Cummings, S. R. (1995). *Ann. Int. Med.* **122,** 9–16.
24. Lindsay, R., Hart, D. M., MacLean, A., Clarke, A. C., Kraszewski, A., and Garwood, J. (1978). *Lancet* **i,** 1325–1327.
25. Christiansen, C., Christensen, M. S., and Transbøl, I. (1981). *Lancet* **i,** 459–461.
26. Gotfredsen, A., Christiansen, C., and Palshof, T. (1984). *Cancer* **53,** 853–857.
27. Love, R., Mazess, R., Tormey, D., Barden, H., Newcomb, P., and Jordan, V. (1988). *Breast Cancer Res. Treat.* **12,** 297–301.
28. Turken, S., Siris, E., Seldin, D., Plaster, E., Hyman, G., and Lindsay, R. (1989). *J. Natl. Cancer Inst.* **81,** 1086–1088.
29. Black, L. J., Sato, M., and Rowley, E. R. (1994). *J. Clin. Invest.* **93,** 62–69.