Estrogen/Progestogen Therapy: Prevention and Treatment of Postmenopausal Osteoporosis (42920)

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In original description of osteoporosis by Albright *et al.* (1), they highlighted the greater prevalence of oophorectomy among patients presenting with osteoporotic fracture, and established for the first time the importance of ovarian failure in the pathogenesis of bone loss. Since that time, considerable evidence has been accumulated documenting the rate of loss of ovarian function in the pathogenesis of osteoporotic fracture (2). This has led to the use of estrogen for prevention of bone loss and subsequent fracture (3) with dramatic success. However, about one decade ago, it became apparent that the uncontrolled use of estrogen in women who had an intact uterus led to an increased incidence of endometrial hyperplasia and malignancy. Concern that a therapeutic regimen that not only might afford protection against osteoporotic fracture, but also might reduce the frequency of ischemic heart disease, might increase the risk of other disorders, has led to a reevaluation of the use of estrogen among the postmenopausal population, and to the development of routes of administration other than the oral, as well as new prescribing habits. This review evalutes the role of estrogen in prevention of osteoporosis as well as summarizes these new attitudes toward the provision of estrogen for the postmenopausal population.

Pathogenesis of Osteoporosis: The Role of Ovarian Failure

The introduction of noninvasive techniques that allow accurate and precise measurement of bone mass enabled study of the asymptomatic process of bone loss that precedes the increase in fracture incidence in the aging population. Early studies, in which peripheral cortical bone was measured, demonstrated that bone mass is fairly constant in women until the fourth and fifth decades when there is a fairly sudden downward trend in bone mass that has been observed in virtually all cross-sectional studies of cortical bone (2). Longitudinal studies confirm that loss of ovarian function coincides with an acceleration of bone loss that seems to last from 3 to 10 years (4). However, when methods for measurement of the axial skeleton were obtained, the situation became somewhat confused, since not all of the data seemed to confirm stability of bone mass among premenopausal women, nor an acceleration at the time of menopause (5). Our own cross-sectional data, obtained using dual photon absorptiometry, suggest that both vertebral bone mass and femoral neck are stable until around 40 years of age and fall thereafter at an average rate of about 2% per annum (Fig. 1). Similar data have been obtained using quantitative computed tomography (6). Johnston *et al.* (7) studying perimenopausal women suggested that the axial trabecular bone might be more sensitive to the gradual decline in ovarian function that occurs in premenopausal women prior to the overt occurrence of ovarian failure, i.e., menopause. Few prospective data have yet to be published across the menopause. However, one group has demonstrated that few women, if any, appear to have significant cortical or trabecular bone loss at the distal radius prior to the onset of ovarian failure (8). The relationship of these data to the cross-sectional studies is not at all clear.

Perhaps the clearest example of the importance of failure in regulating the changes that occur with age is the experiment of Richelson *et al.* (9). This group demonstrated clearly that bone mass in women after the onset of ovarian failure was more closely related to the duration of estrogen deficiency than to chronologic age.

Biochemical studies confirm that the loss of ovarian hormones is associated with profound changes in calcium metabolism. Urinary calcium and hydroxyproline increase, as does plasma alkaline phosphatase and bone GLA-protein (osteocalcin). These changes are taken to be indicative of increased skeletal remodeling. Indeed, using the calcium balance technique, coupled with kinetic data, Heaney *et al.* (10) have demonstrated that skeletal remodeling does increase in estrogen-deficient women and there is a widening of the gap between

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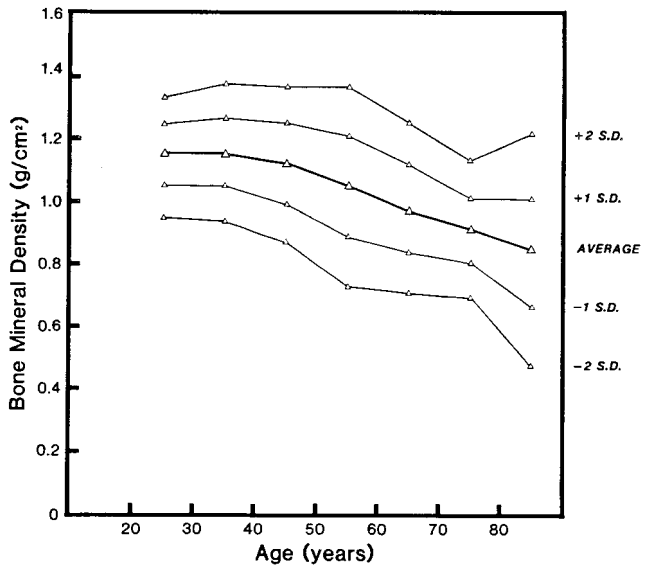

Figure 1. Bone mass in lumbar vertebrae (L2-4) in normal healthy Caucasian women aged 29–90 years (n = 420). Measurement by dual photon absorptiometry (Lunar DP3).

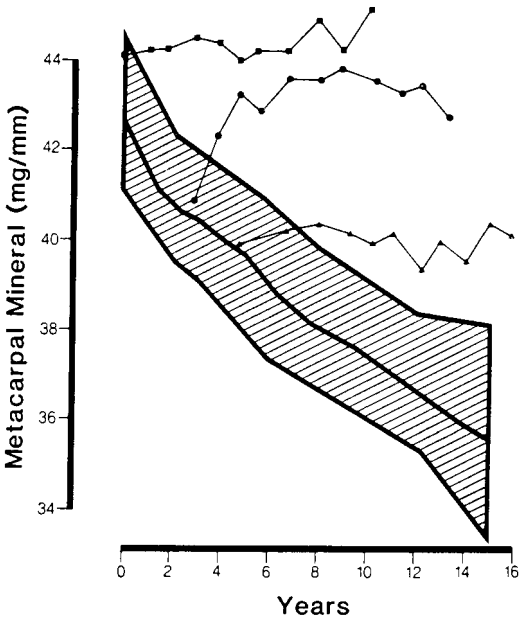

Figure 2. The effects of mestranol on bone mass in three groups of women in whom treatment was begun immediately, 3 years or 6 years after bilateral oophorectomy. The hatched area represents the pattern of bone loss in the placebo-treated group (mean ± SD), while only the means of the three estrogen-treated groups are shown (from reference (11)).

formation and resorption. There is consequently increased release of calcium from bone to blood accompanied by a decline in intestinal calcium absorption, while urinary loss of calcium increases. These changes culminate in negative calcium balance and bone loss. The initial event precipitating these changes is still debated, but seems likely to be a primary change in skeletal remodeling and the change in calcium homeostasis a secondary response. However, the predicted changes in the regulatory hormone systems, particularly parathyroid hormone and the vitamin D system, have been difficult to measure. It is possible that this reflects difficulties with the sensitivity of the assay systems within the normal range.

Effects of Estrogen

Numerous data now indicate that estrogen intervention prevents bone loss in postmenopausal or oophorectomized women (see reference (2) for review). Our long-term data (11) indicate that estrogens prevent bone loss, irrespective of the time after oophorectomy (Fig. 2). The effects persist for as long as estrogens are prescribed, at least 10 years, and bone loss begins again when estrogens are discontinued. The rate of bone loss after estrogen withdrawal is identical to that after sudden cessation of ovarian function, as at oophorectomy, and this perhaps, finally, confirms the close relationship between sex steroids and the skeleton.

Many studies have appeared confirming the potent effects of estrogen on the skeleton in postmenopausal women. Dose ranging studies have shown that early to mid-follicular levels of estradiol are required to produce the biochemical changes that are considered to be markers of the reduction in bone remodeling that characterizes estrogen administration. Circulating levels of around 40 pg/ml of 17β-estradiol appear to be sufficient to cause a fall in urinary calcium and hydroxyproline (12) and perhaps to prevent trabecular but not cortical bone loss (8). These data are compatible with the studies published in which the effective dose of conjugated equine estrogens (Premarin) was determined over a 2-year period using bone mass measurements. Both studies indicated that 0.625 mg of conjugated equine estrogen was sufficient to produce the maximum reduction in bone loss with a sufficiently steep dose response were such that no effect is evident at 0.15 mg/day (13). Since the primary effect of estrogen is inhibition of resorption, no added effects are seen if the dose is pushed beyond 0.625 mg/day.

The mechanism of the effect of estrogens on the skeleton remains obscure. Until recently, the inability to demonstrate estrogen receptors in skeletal cells made an indirect mechanism of action the most plausible. The suggestion that circulating calcitonin levels were lower in women than in men and that calcitonin secretion could be stimulated by estrogen created a mechanism for estrogen action of the skeleton, since calcitonin is a direct inhibitor of osteoclast action. However, direct stimulation of calcitonin secretion *in vitro* by estrogen occurs at supraphysiologic doses. During the past year, two groups have demonstrated the presence of estrogen receptors on osteoblasts or osteoblast-like cell lines (14, 15). In addition, responses of osteoblast cell lines including reduction in growth rate and increased production of alkaline phosphatase and collagen have been

demonstrated after addition of physiologic concentrations of estrogen. Thus, we now have a potential mechanism for interaction of the sex steroids directly with skeletal cells. However, the principal effect, when estrogens are given to postmenopausal women, is reduction in bone resorption. Estrogen must, therefore, inhibit the activity of osteoclasts or their recruitment. Effects on the osteoclast are difficult to demonstrate *in vitro.* Although bone resorption can be inhibited by estrogen, the response is seen only at supraphysiologic doses, even in systems which have functioning osteoblasts. The reason for this is still obscure. At the very least, therefore, for a direct skeletal effect of estrogen there requires to be a second messenger generated by the osteoblast that acts on the osteoclast. Although several local candidates exist as stimulators of bone resorption (interleukin 1 for example is one of the most potent stimulators of resorption), no local inhibitors are known nor are any of the stimulators produced by osteoblasts but rather by cells of the monocyte-macrophage series. Curiously, interleukin 1 production in peripheral monocytes has been reported to be elevated in patients with postmenopausal osteoporosis, as well as after oophorectomy, with suppression of production after the addition of estrogen (16). This raises the tantalizing possibility that the interleukins and perhaps also other cytokines are involved closely in the physiologic remodeling process. However, much further work is required to unravel the local control processes, as well as the medications in the estrogen effects.

Estrogen Effects on Fracture

No prospective study has been able to determine the effects of estrogen on fractures among the elderly. However, several retrospective and case control studies have shown a reduction in the risk of hip fracture (See reference (2) for review). There is a remarkable consistency in these studies, all suggesting that hip fracture frequency will be halved, reducing hip fracture frequency in the aging female to the level that occurs among men. Recognizing the difficulty in retrospectively defining the exact estrogen exposure in aged patients, it is remarkable that all studies have been able to demonstrate a reduction in fractures. The data also suggest that the earlier in the postmenopausal period estrogens are used, the more beneficial the effect will be on fracture risk. This we would predict, knowing that estrogens functionally behave as antiresorptive agents and will therefore simply reduce the rate of bone loss. Clearly, therefore, the more beneficial effects would be expected in patients with higher baseline bone mass; i.e., those closer to the menopause.

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1. Albright F, Bloomberg F, Smith PH. Postmenopausal osteoporosis. Trans Assoc Am Physicians **55**:298–305, 1940.
2. Lindsay R. Sex steroids in the pathogenesis and prevention of osteoporosis. In: Riggs, BL Ed. Osteoporosis: Etiology, Diagnosis and Management. Raven Press: New York, pp333–358, 1988.
3. Ettinger B, Genant HK, Cann CE. Long-term estrogen therapy prevents bone loss and fracture. Ann Intern Med **102**:319–324, 1985.
4. Lindsay R, Aitken JM, Anderson JB, Hart DM, MacDonald EB, Clark AC. Long-term prevention of postemenopausal osteoporosis by oestrogen. Lancet **1**:1038–1041, 1976.
5. Riggs BL, Wahner HW, Dunn WL, Mazess RB, Offord KP, Melton LJ III. Differential changes in bone mineral density of the appendicular and axial skeleton with aging: Relationship to spinal osteoporosis. J Clin Invest **67**:328–335, 1981.
6. Cann CE, Genant HK, Kolb FO, Ettinger B. Quantitative computed tomography for prediction of vertebral fracture risk. Bone **6**:1–7, 1985.
7. Johnston CC, Hui SL, Witt RM, Appledorn R, Baker RS, Longcope C. Early menopausal changes in bone mass and sex steroids. J Clin Endocrinol Metab **61**:905–911, 1985.
8. Slemenda C, Hui SL, Longcope C, Johnston CC. Sex steroids and bone mass. J Clin Invest **80**:1261–1269, 1987.
9. Richelson LS, Wahner HW, Melton LJ, Riggs BL. Relative contributions of aging and estrogen deficiency to postmenopausal bone loss. N Engl J Med **311**:1273–1275, 1984.
10. Heaney RP, Recker RR, Saville PD. Menopausal changes in bone remodeling. J Lab Clin Med **92**:964–970, 1978.
11. Lindsay R, Hart DM, Abdalla H, Al-Azzawi F. Interrelationship of bone loss and its prevention and fracture expression. In: Christiansen C, Johansen JS, Riis BJ, Eds. Osteoporosis, Osteopres. Copenhagen, Denmark, pp508–512, 1987.
12. Selby PL, Peacock M. Dose dependent response of symptoms, pituitary and bone to transdermal oestrogen in postmenopausal women. Br Med J **293**:1337–1339, 1986.
13. Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss. Obstet Gynecol **63**:759–763, 1984.
14. Eriksen EF, Colvard DS, Berg NJ, *et al.* Evidence of estrogen receptors in normal human osteoblast-like cells. Science **241**:81–85, 1988.
15. Komm KB, Terpening CM, Benz DJ, *et al.* Estrogen binding receptor mRNA and biological response in osteoblast-like cells. Science **241**:81–86, 1988.
16. Pacifici R, Rifas L, Vared I, *et al.* Interleukin-1 secretion from human blood monocytes in normal and osteoporotic women: Effect of menopause and estrogen/progesterone treatment. J Bone Miner Res **3(suppl)**:541, 1988.