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*Review Article*

# Estrogens, Bone Loss and Preservation

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## Estrogens

Estrogens can be defined as compounds that are able to produce vaginal cornification or uterotrophic effects in oophorectomized rats or mice [1]. Estrogens are divided into four main groups:

1. Synthetic estrogen analogues without a steroid skeleton, such as stilboestrol and its derivatives
2. Synthetic estrogen analogues with a steroid skeleton
3. Non-human estrogens, produced from horse urine (conjugated estrogens)
4. Human estrogens or compounds that are transformed to human estrogens in the body.

The potency of different estrogens is variable. In addition, bioassays used to determine potency do not necessarily give the same potency ratio. This indicates estrogens have qualitative differences as well as differences in absolute potency [1,2]. Studies indicate that non-synthetic estrogens produce less metabolic side effects than do synthetic estrogens [3].

Synthetic estrogens without a steroid structure are no longer used, except as estrogen inhibitors (tamoxifen, clomiphene). Synthetic estrogens with a steroid structure, i.e., ethinyloestradiol, are still the most frequently used estrogen in oral contraceptives. For postmenopausal therapy the conjugated equine estrogens are the most common in the United States, whereas in Europe there has been a tradition for using human estrogens (i.e., 17beta-oestradiol or its esters).

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## Progestins

Substances described as progestins (progestagens and gestagens) differ greatly in their properties, but have at least one property in common – they are all able to cause secretory transformation of an endometrium in which estrogen-induced proliferation has occurred [4]. In addition to this effect, progestins may have estrogenic, anti-estrogenic, androgenic, anti-androgenic, antigonadotrophic, glucocorticoid-like, and ACTH stimulating activities. Progestins may be divided into two subgroups: (1) 19-nortestosterone derivatives, with a relatively high androgenic effect; and (2) 17-hydroxyprogesterone derivatives, with less androgenic effect. Finally, natural human progesterone is available in a micronized form for oral therapy.

## Mechanism of Bone Loss After Menopause

Cross-sectional data, originally obtained in the peripheral skeleton, suggest the bone mass is stable in adult women (see Anderson et al. this issue) until around the time of ovarian failure when bone loss begins in almost all women [5–20]. The temporal association between declining bone mass and cessation of ovarian failure has been taken as confirmation of Albright's original hypothesis [21,22] that osteoporosis occurs because of the estrogen deficiency state produced by cessation of ovarian sex steroid secretion.

While more recent data, in which the axial skeleton has been measured, tend to confirm the original observations [23,24], a few studies, also cross-sectional in design, have shown a more continuous pattern of declining bone mass from early in the third decade [25,26].

These studies are in the minority, however, and generally suffer from inadequate sample size or analysis. Most recently, data from at least two centers do suggest that there is significant premenopausal bone loss from the femoral neck, with only modest acceleration in the rate of loss after menopause [27,28]. This is unlike the behavior of bone in the spine or periperhal sites of measurement in which bone mass is stable at least until the fifth decade.

Longitudinal data now confirm for both peripheral cortical bone and bone in the spine, some premenopausal bone loss in the fifth decade related to gradually declining ovarian function [29]. The rate of loss is related to the endogenous supply of estrogen confirming our original data that demonstrated that in older postmenopausal women the rate of bone loss was also related to the remaining supply of endogenous estradiol [30]. These data also suggest strongly the cause and effect relationship between estrogen supply and negative bone balance.

In a series of studies using the techniques of calcium kinetics combined with balance data, Heaney demonstrated increased movement of calcium into and out of the skeleton after menopause, coupled with a decline in calcium absorption across the intestine and increased calcium loss from the body principally through the kidney [31–33]. These studies indicate that there are intrinsic alterations in skeletal metabolism that occur with ovarian failure, rather than changes imposed upon the skeleton by alterations in calcium handling by the organism. Following loss of ovarian function, biochemical data also show evidence of increased skeletal turnover [34,35]. Indices of bone formation (alkaline phosphatase, osteocalcin) increase as do indicators of bone resorption (excretion of hydroxyproline and deoxypyridinoline) [Fig. 1].

To understand how such changes in skeletal metabolism can result in net loss of bone tissue, it is important to have some concept of the cellular processes thought to be involved in bone remodeling in the adult human. Remodeling of bone occurs in small packets in both cancellous and cortical bone [36]. A local signal, about which little is understood, activates the remodelling process, and recruits osteoclasts to the site. The team of osteoclasts resorb the bone by dissolving mineral into an extracellular acid environment, and enzymatically digesting the organic matrix. In cancellous bone, after the osteoclast team have resorbed an apparently preset volume of bone these cells are replaced by monocytic cells whose function is unknown, but in some way may prepare the surface and assist in the recruitment of a team of osteoblasts which are responsible for replacing the resorbed tissue with newly formed bone. In a properly balanced homeostatic system the amount of bone laid down by the osteoblast team exactly matches the amount removed by the osteoclasts. However, histological evidence suggests that there is an age-related decline in the amount of bone formed compared to that resorbed at each remodelling cycle and that this inequity is increased after ovarian failure. In addition, it has been proposed that following menopause the osteoclasts become hyperactive and penetrate too deeply into the trabecular plates, perforating them. The compound effects of increased osteoclasts and declining osteoblastic function are exacerbated by an increase in the frequency with which new remodeling cycles are activated after menopause, leading to the postmenopausal acceleration of bone loss.

The consequence of these changes in skeletal homeostasis in cancellous bone is the thinning and complete eradication of trabecular structures [36, 37]. As far as we are aware no mechanisms exist for replacement of these structures once they have been destroyed. Discontinuity in the trabecular pattern by itself creates a therapeutic problem since increasing the width of disconnected trabeculae would not alter the basic biomechanical strength of the overall structure. Thus, prevention is the most effective approach to the treatment of osteoporosis, and is likely to remain so.

Since bone remodeling is a surface phenomenon, as

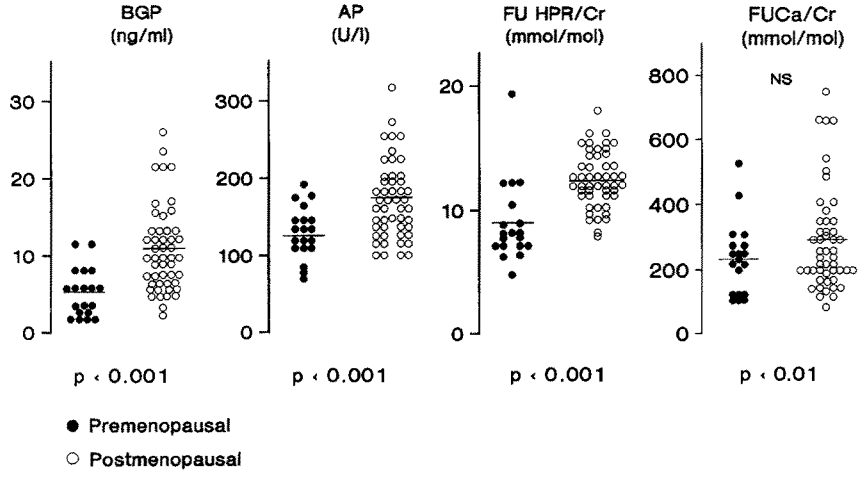


**Fig. 1.** The effect of estrogen deficiency on biochemical indices of bone turnover. In postmenopausal women the bone formation (plasma BGP and alkaline phosphatase) and bone resportion (urinary calcium and hydroxyproline) are increase compared with premenopausal women.

trabeculae are removed the surface available for further remodeling cycles is reduced and the rate of remodeling activation declines. Thus the absolute magnitude of bone loss declines with menopausal years.

It is still not entirely clear if those likely to develop osteoporosis are those entering menopause with low bone mass or those whose accelerated phase of bone loss persists for longer than average (see Hui et al. this issue, p. 30). The fact that bone mass is predictive of future fractures suggests that initial mass is at least in part indicative of those at risk. In addition, biochemical evaluation of rate of loss has providen useful in determining subsequent bone loss for at least up to 11 years. Thus a combination of bone mass with biochemical indices of turnover may be the most effective method for prediction of those at risk.

## Generalized Effects of Postmenopausal Hormonal Therapy

### *Estrogens*

Postmenopausal estrogen therapy is most often instituted to ameliorate climacteric symptoms. All estrogens and routes of administration (oral, vaginal or parenteral) [38,39] are effective. In addition, estrogen therapy has a number of other effects, e.g., it prevents atrophy of the skin [40], mucous membranes [41], and urogenital tract.

Epidemiological studies have shown that postmenopausal estrogen therapy prevents osteoporosis [42–44] and probably also decreases the incidence of cardiovascular disease [45–47].

### *Progestins*

Progestins alone are rarely used for postmenopausal hormonal therapy, but may be an alternative in specific cases where estrogen therapy is contra-indicated. Only some progestins are able to ameliorate the subjective climacteric symptoms [48] and bone loss [49,50]. The latter subject has not, however, been as thoroughly investigated as have the effects of estrogen, probably because the progestins when given without estrogens produce a variety of undesirable side effects.

### *Estrogen–Progestin Combinations*

Estrogen–progestin combinations have the same effect on subjective symptoms, skin, and mucous membranes as unopposed estrogens. Progestins do not counteract the estrogenic effect on bone loss and osteoporosis [51,52]. The effect of combined therapy on cardiovascular disease is still not clarified.

## Effects on Bone

Postmenopausal bone loss is principally estrogen dependent and is prevented by estrogen substitution therapy [43,49,51–57]. Other factors, such as calcium deficiency, may aggravate postmenopausal bone loss, but correction of these factors will only modestly reduce bone loss. The effects of estrogen or estrogen–progestin therapy on bone are seen independent of age and menopausal age [58–61]. In early postmenopausal women oral estrogen and estrogen–gestagen regimens, both synthetic and non-synthetic, reduce bone loss [43,51,53,54,62,63] although non-synthetic estrogens are preferred for postmenopausal therapy. The estrogenic effect on bone is dose-dependent, indicating that if a sufficient serum concentration of estrogen is *not* obtained, bone loss will *not* be arrested. For oral estrogen and estrogen–progestin therapy, studies have demonstrated that doses of 0.625 mg of conjugated estrogens, or 2 mg of 17B-estradiol are optimum for prevention of early postmenopausal bone loss [64,65] (Fig. 2). Postmenopausal bone loss is a generalized phenomenon that affects all parts of the skeleton, i.e., both areas with mainly trabecular bone (e.g., the spine) and areas with mainly cortical bone (e.g., the forearm and the hip) [66,67]. Postmenopausal estrogen therapy prevents correspondingly the bone loss from all skeletal areas (Fig. 3), including loss occurring in the skull,

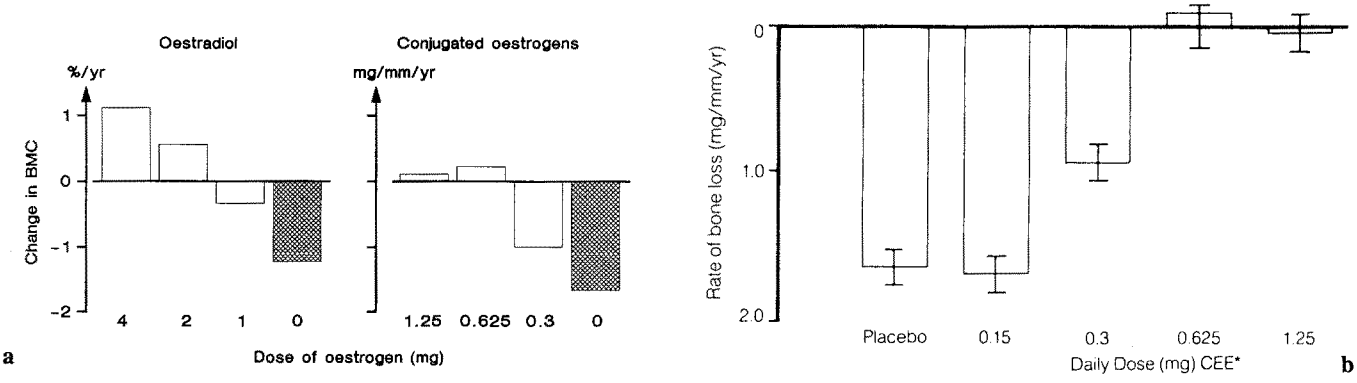


**Fig. 2.** The effect of different doses of estrogens on loss of bone mineral. The optimum bone sparing dose of estradiol lies between 1 and 2 mg daily, and is 0.625 mg daily for conjugated estrogens. (From references 64, 65 with permission.)

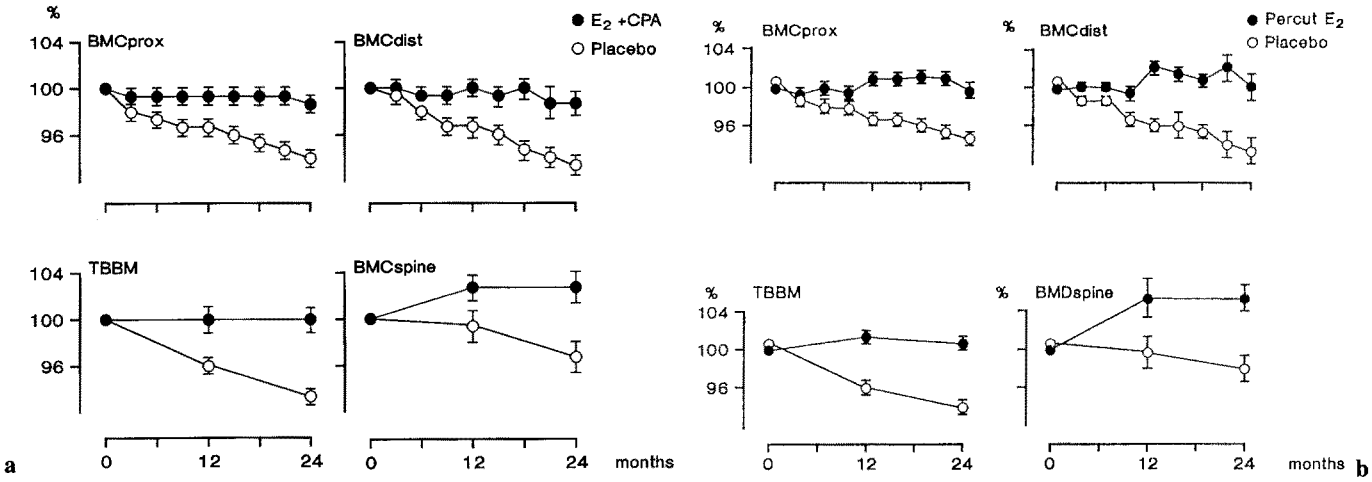


**Fig. 3.** Bone mass measured in different areas of the skeleton during therapy with oral estradiol ($E_2$) or percutaneous estradiol or placebo. Note that both oral and percutaneous estradiol prevents the bone loss in all skeletal areas.

chest, arms, pelvis, and legs [67], as well as spine, hip and forearm [66,67].

In addition to oral therapy, new delivery systems are available in which estrogens can be given across the skin as percutaneous 17B-estradiol (Fig. 3) i.e., estradiol given in a gel to be applied every day on the skin [57] or as transcutaneous estradiol, i.e., estradiol given in a patch to be changed twice a week. Preliminary studies have demonstrated that this latter delivery system also prevents bone loss [68], and double-blind controlled studies are expected shortly.

## Estrogen Therapy Later in Life

Increased bone turnover seems to be most pronounced in the early postmenopausal years. With increasing menopausal age there may be a tendency towards a reduction in bone turnover, and thereby in rate of bone loss. The greatest benefit from estrogen therapy is, therefore, obtained if instituted shortly after menopause. Indeed, it has been disputed whether estrogens have any effect in elderly postmenopausal women. However, the literature contains clear evidence that estrogens prevent bone loss in all stages of postmenopausal life, at least up to an age of 70 years [58–61] (Fig. 4).

## Effects on Fractures

When estrogen therapy is stopped bone loss recurs, at a rate equivalent to that occurring after oophorectomy [52,69]. Several epidemiological studies have shown that estrogen provides protection against fracture [42,44,70–73]. However, it is obvious that the treatment has to be continued for some years to be effective. It is difficult to suggest a definite treatment time, but 5–10 years may be necessary before this fracture protection can be observed, the assumption being made that estrogens are provided in the immediate postmenopausal period. Reduction in fracture risk probably occurs at all skeletal sites, especially femoral neck, and one controlled long-term study demonstrated a reduction in vertebral deformity on radiography by 90% [10]. Thus estrogen remains the agent best documented to prevent postmenopausal osteoporosis.

## Estrogen and Calcium

The role of calcium intake in development of low bone mass and susceptibility to fractures is still intensely debated. In large parts of the Western world, the daily calcium intake approximates 500 mg. One series of studies of calcium metabolism has indicated a daily requirement of 1000 mg of calcium for premenopausal women and 1500 mg for postmenopausal women [31–33], in order to maintain calcium balance. Moreover, those studies and others suggested that a sufficiently high calcium intake might reverse a negative calcium balance and, thereby, suppress bone loss. However, this has not been confirmed in longitudinal double-blind studies of early postmenopausal women [55,56,74,75].

Since the adverse effects of estrogen therapy are dose-dependent, it would, therefore, be of major importance if it were possible to reduce the dose of estrogen required to prevent the bone loss and osteoporosis. A recent study suggested that the dose of estrogen could be reduced by 50% if it was combined with a daily calcium supplement of 1000 mg [76]. The study was not double-blind, placebo controlled, and will require to be confirmed by future well-controlled studies before final conclusions can be drawn. One other study was examined whether a calcium supplement would give additional benefit to an already optimized estrogen regimen [77]. However, in that study estrogen alone proved as effective as estrogen combined with calcium.

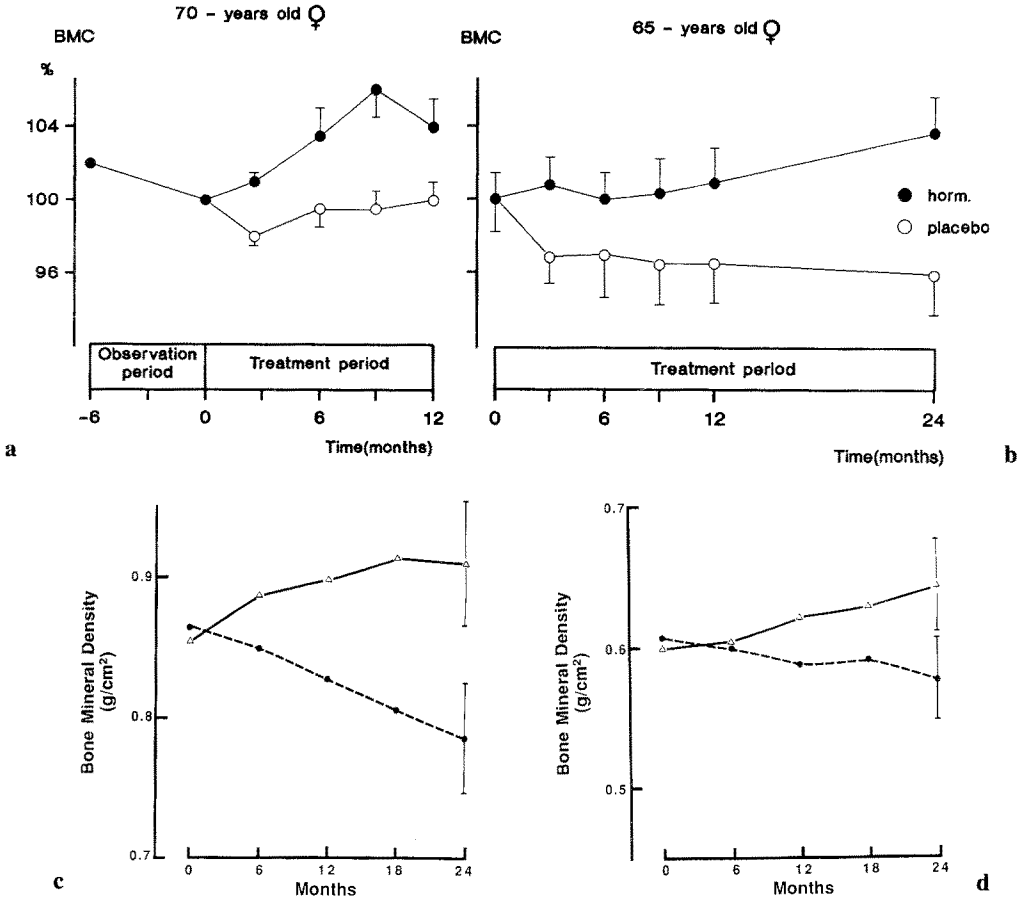


**Fig. 4a–d.** Bone loss is prevented in postmenopausal women independent of age and menopausal age. The figure illustrates that older women aged up to 70 years treated with female hormones have their bone loss prevented efficiently. Panels **a** and **b** demonstrate effects at 65 and 70 years. Panels **c** and **d** represent the effects of estrogen (open symbols) on spine and femoral neck respectively in women with osteoporosis. (From reference 61 with permission.)

## Mode of Action

As we have noted Heaney demonstrated increased bone remodelling after menopause [31–33]. In the same series of studies estrogen therapy was shown to reverse this effect. In addition to reduction in the flow of calcium into and out of bone, there was evidence of improved absorption of calcium across the intestine, and reduced loss of calcium in urine. The mechanism by which this improved efficiency in calcium utilization is effected by estrogen remains obscure. It has proved remarkably difficult, in part related to technical problems, to demonstrate that specific receptors from estrogen exist within the skeleton, and that the bone cells were, therefore, target cells for estrogens. Consequently, mechanisms for indirect action have been sought. The most popular suggestion has been that estrogen increases the secretion of calcitonin [78], for which in vitro data exist [79]. Since the major effect of calcitonin, when used pharmacologically, has been the reduction of osteoclast activity and perhaps also recruitment, it was not difficult to propose that increased endogenous calcitonin secretion in response to estrogen was responsible for inhibition of bone resorption. However, no data have demonstrated that changes in calcitonin secretion within the normal range have significant effects on bone resorption. The data that are available tend to support the concept that estrogens inhibit the effect of parathyroid hormone on bone, a concept enunciated many years ago by Heaney [80]. Recent evidence that there may be estrogen receptors on cells from bone [81, 82] suggests that this may be mediated directly. Two groups have demonstrated that high affinity receptors for estradiol exist on certain clones of cells originating from osteoblasts. Data also indicate that PTH acts primarily on osteoblasts, suggesting that interactions between the hormones could occur at the level of these calls. Osteoblasts, therefore, may be key in control of bone remodeling and resorption. A detailed review of the possible cellular mode of action of estrogen will follow in a later issue.

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