The Effect of Estrogens in Prevention and Treatment of Osteoporosis

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Osteoporosis is a disorder of the skeleton characterized by reduction in skeletal mass and a consequent alteration in architecture that increases the risk of fracture (1). The disorder is most evident among postmenopausal women, as Albright pointed out more than 50 years ago (2). In many countries osteoporosis has now been recognized as a major public health problem. It has been estimated that in the United States there result some 1.5 million fractures each year at a cost of $10 to $20 billion (3). An increase in the number of fractures is occurring as the population ages, and in some countries there appears to be an increase in age-specific incidence of the disorder, for reasons that are unknown.

PATHOPHYSIOLOGY

The amount of bone in the skeleton in the young adult is primarily under genetic control, but may be modified during growth by diet and physical activity. Peak bone mass, as this is called, is greater in men than in women (4). In addition, women begin to lose bone tissue as they approach menopause, or if ovarian failure occurs for any other reason (5). Thus, bone loss with age is ubiquitous among the female of the human species. The rate of loss of bone is greatest in areas of cancellous bone, the spongy bone that forms the center of vertebral bodies, and also occurs at other sites such as within the femoral neck. It is not surprising, therefore, that the most frequent fractures are those of the spine (so-called crush fractures) and hip, although fracture of any bone can occur (3).

Bone mass after menopause therefore depends on initial bone mass and rate of loss. Bone loss, while primarily occurring because of reduction in the supply of ovarian sex steroids, can be modified by a wide variety of other factors, often called risk factors. The most commonly cited risk factors are listed in Table 1.

Nutritional status contributes to skeletal status in several ways, but does not appear to influence significantly the rate of bone loss in the period immediately after menopause (6). Reduced calcium intake can clearly cause bone loss, principally by
ESTROGENS AND OSTEOPOROSIS

TABLE 1. Proposed risk factors for osteoporosis

<table>
<thead>
<tr>
<th>Genetic</th>
<th>High sodium</th>
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<tbody>
<tr>
<td>Race</td>
<td>High animal protein</td>
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<tr>
<td>Sex</td>
<td>Lifestyle</td>
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<tr>
<td>Familial prevalence</td>
<td>Cigarette use</td>
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<tr>
<td>Nutritional</td>
<td>Low physical activity</td>
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<td>Low calcium intake</td>
<td>Endocrine</td>
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<tr>
<td>High alcohol</td>
<td>Menopausal age (oophorectomy)</td>
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<tr>
<td>High caffeine</td>
<td>Obesity</td>
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</table>

necessitating the use of skeletal calcium to maintain serum calcium constant in the presence of inadequate dietary supply. In the immediate phase after menopause, release of calcium from the skeleton is increased as estrogen levels decline, thereby allowing serum calcium to be sustained even when calcium intake is quite low. Consequently, calcium supplementation does not significantly reduce bone loss at this time of life, especially at sites of cancellous bone. A diet deficient in calcium is generally poor in other nutrients (RP Heaney, personal communication). Several nutritional abnormalities may also interfere in a negative way with skeletal homeostasis, including anorexia and bulimia as well as excess caffeine, alcohol, and possibly protein intake.

Gradual decline in physical activity with increasing age is also a contributor to bone loss. The skeleton can be considered to have a “mechanostat” that responds to the level of use (7). Thus, increasing use results in increments of skeletal mass. The converse is also true. One other lifestyle factor that may affect the skeleton is cigarette consumption, although the importance of this is not entirely clear.

In addition to nutritional and lifestyle factors, there are a variety of sporadic factors including excess thyroid hormone, glucocorticoid use, or excess endogenous production that can negatively affect the skeleton. The effects of all these risk factors are likely to be additive and cumulative in any individual, but cannot be used to assess accurately risk or skeletal status in the individual patient.

The availability of non-invasive techniques for measurement of bone mass has improved the capacity to estimate individual risk (8). Low bone mass is the single most important risk factor for fracture. Recent data have shown that low bone mass predicts not only future bone mass but also the risk of future fracture (8). Thus, a single estimate of bone mass can be used as a guide to determine those requiring preventive therapy.

PREVENTION

It is perhaps not surprising that if loss of ovarian hormones increases the rate of bone turnover and loss of skeletal tissue, replacement of those hormones reverses this effect (5,9). Many studies have now shown that estrogen intervention reduces the rate of bone loss in either postmenopausal women or ovariectomized women.
The effects can be seen immediately after loss of ovarian function and at least up to the age of 75 years (10) and in patients with established osteoporosis. The action of estrogen in slowing bone loss continues for as long as therapy is continued, and when treatment is stopped there is a corresponding increase in bone remodeling and bone loss begins again (11). The skeleton is extremely sensitive to the effects of estrogen and dose levels that supply sufficient estradiol to achieve mid-follicular serum levels appear to be capable of slowing bone loss. For conjugated equine estrogens, two studies have demonstrated that the minimum effective dose is 0.625 mg and that there is no advantage to increasing the dose further (12,13). The skeleton does not appear to be concerned about the route of administration, only the adequacy of the supplied dose, and estrogens given by any route that have been tested slow bone loss if adequate circulating concentrations can be achieved.

Long-term estrogen use, at least more than 5 years, is associated with a reduction in the risk of fractures of the hip and distal radius (5,14). Data also indicate that estrogens reduce the risk of vertebral crush fracture, possibly by as much as 75% (15,16). Thus, estrogen therapy would be expected to reduce significantly the impact of osteoporotic fractures among the aging female population. It is still not clear if these effects will persist after treatment is discontinued and it may be that to obtain maximum benefit, long-term, if not lifetime, therapy will be required.

Certain progestins also reduce bone turnover and the rate of bone loss. Those most commonly found to be effective belong to the class of progestins derived from 19-nortestosterone, and may be related to their androgenic or anabolic effects rather than to progestin activity (17). In most studies, the addition of a progestin to estrogen, used to protect the endometrium from long-term continuous exposure to estrogens, does not significantly influence the effect of estrogen on the skeleton. Recently, one study suggested that the addition of 1 mg per day norethindrone to an estrogen results in a more positive bone balance than could be achieved by estrogen alone (18). This study requires to be confirmed.

Other potential interactions of estrogen include those with the nutritional and lifestyle risk factors. One study suggests that the required estrogen dose can be reduced in the presence of a moderately high calcium intake of 1,500 mg/day (19). Another study indicates that the effects of estrogen on bone mass are greater when coupled with a resistance exercise program (20). Finally, published data suggest that estrogen metabolism may be altered by cigarette consumption to a degree that negatively affects the skeletal response (21). All of those data require further study.

**Side Effects of Estrogen**

The long-term exposure to estrogen significantly increases the risk of endometrial carcinoma (22). Daily doses of 0.625 mg of conjugated equine estrogen at least double the risk (an increase from 1:1,000 patient years to 2:1,000), whereas doubling the daily dose increases the risk from 4 to 8 times over baseline. The addition of a progestin reverses this effect. Progestins are most commonly provided in sequential
fashion with 12 to 14 days of treatment each month. Our usual regimen is daily estrogen, 0.625 mg conjugated equine estrogen, on a continuous basis and medroxyprogesterone acetate 5 to 10 mg/day from day 1 through day 14 of each calendar month. This regimen results in monthly vaginal bleeding that is usually somewhat lighter than a regular period. If breast tenderness is a problem, estrogen can be omitted from day 14 of each month for 3 to 7 days. For those who prefer to avoid bleeding, if the patient is more than 3 years from menopause, a regimen of continuous therapy can be attempted (23). The usual is a combination of 0.625 mg conjugated equine estrogen in combination with medroxyprogesterone acetate 2.5 mg per day. In about 60% of cases or more vaginal bleeding ceases within 6 months and does not recur. The long-term safety of this regimen has yet to be tested adequately.

The most serious potential side effect of hormone therapy of postmenopausal women is the chance of an increase in the risk of breast cancer (24). The data are extremely mixed. Recent attempts at meta-analysis of the studies available suggest a small (10–20%) increase in risk associated with long-term therapy (>10 years) (25). The effect of the added progestin is not clear, and progestin may further increase the risk. For that reason, among others, progestins should not be used in the absence of a uterus. Since breast cancer is very common, there is good reason for ensuring that every postmenopausal woman have an annual mammography. There are no studies that indicate an increase in the mortality from breast cancer with estrogen use. There is a small but significant increase in the risk of gallstones associated with oral estrogen administration.

Estrogen administration to postmenopausal women appears to reduce the risk of ischemic heart disease significantly (26). Several epidemiological studies have examined this in detail. The general conclusion appears to be that long-term estrogen use is associated with a reduction in risk of about 50%, an extraordinary rate of protection if indeed it is accurate. There are potential mechanisms of action for this effect of estrogen. First, there is a clear increase in low-density lipoprotein across the menopause, an effect that is reversed by estrogen. Additionally, oral estrogens increase the circulating concentration of high-density lipoprotein (27). These are considered to be beneficial effects on lipoprotein metabolism, which might at least in part account for the effects on cardiac disease. In addition, estrogens are known to have receptors in arterial walls, and the physiological responses of coronary arteries are dependent on estrogen status (28). Vasodilator responses to physiological stimuli are changes to vasoconstrictor responses in the absence of estrogen. In animal models of coronary disease. Reduction in risk of cardiovascular disease will clearly outweigh all other effects of postmenopausal estrogen. The effect of added progestin is still not clear since progestins at least to some extent reverse the effects of estrogen on lipoprotein metabolism. One epidemiological study suggests that progestins do not significantly alter the estrogen effects, but clearly confirmatory studies are required.

Mode of Action of Estrogen

The mode of action of estrogen on the skeleton remains obscure. Recently, estrogen receptors have been found in cells of the osteoblast lineage (29). A variety
of physiological responses have been described in vitro in response to incubation with biologically appropriate concentrations of estrogen. These include alteration in cell division, increased expression of the RNA of a variety of proteins known to be synthesized by osteoblasts including type I collagen, alkaline phosphatase, TGF-β, IGF-1, and osteocalcin. Others have been unable to detect significant responses in osteoblast-like cells unless transfected with estrogen receptors. Recently, one study could find no effects on primary cultures of human osteoblasts (30). Alternative actions of estrogens include the potential for steroids to mediate their effects on skeletal metabolism by affecting cells within marrow not normally considered to be directly involved in skeletal remodeling. Alterations in mast cell activity, or production of interleukins by cells of the monocyte macrophage series, are potential mechanisms for estrogens to affect skeletal homeostasis. Further studies of the direct effects of estrogens are required.

Estrogens could also modify skeletal remodeling by interacting with calcium homeostasis. Recently, we demonstrated that estrogens altered parathyroid sensitivity and increased the hydroxylation of 25-hydroxyvitamin D to its active metabolite 1,25-dihydroxyvitamin D. Increased production of this metabolite could account for the improved intestinal calcium absorption observed after estrogen administration (31). In part at least this may also explain the improved efficiency in utilization of nutritional calcium and thus the reduced calcium requirement to maintain calcium homeostasis, which appears to be about 1,000 mg/day, or 500 mg less than the daily requirement of estrogen-depleted women.

Alternatives to Estrogen

Alternatives to estrogen for prevention of bone loss are limited. Salmon calcitonin given either by subcutaneous or intranasal route can slow bone loss in the immediate postmenopausal period (32). Alterations in nutrition or physical activity cannot slow bone loss, but may potentially modify individual response to estrogen and must be considered when estrogens are used. There are limited data that suggest that bisphosphonates may also prevent bone loss, but insufficient data are available about the long-term effects of these medications for them to be recommended for use as preventive therapy.

Treatment of the established condition (i.e., after fracture has resulted in presentation of the patient to the clinician) allows the clinician limited choices. Estrogens are again first-line therapy. Calcitonin is an alternative, and potentially bisphosphonates can also be used. All of those agents, although acting through different mechanisms, reduce bone remodeling. Therefore, these agents are most likely to be effective in situations of increased turnover. When patients present after fracture, bone remodeling is only increased in the minority. However, in general most individuals appear to do relatively well when estrogens or calcitonin are used, although some data suggest that the response is somewhat better when high turnover can be documented. As yet there are no agents that increase bone formation and reliably
reduce the risk of recurrent fracture, and the disorder is more easily prevented than treated.

CONCLUSION

Estrogen loss at the time of menopause (or at any time of life) increases skeletal remodeling and accelerates bone loss. Estrogen replacement prevents this process and reduces the risk of future fracture. The effects of estrogen in this regard are specific. Alteration in nutrition or physical activity cannot replace the effects of estrogen in the immediate years after menopause, but potentially may modify individual response to estrogen. Estrogens can also be used in treatment of the established disease. In addition to their effect on bone, estrogens also appear to reduce the risk of cardiovascular disease among postmenopausal women, but may increase the risk of breast cancer after prolonged use. Estrogen use is associated with an overall reduction in mortality among postmenopausal women.

ACKNOWLEDGMENTS

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REFERENCES


**DISCUSSION**

This chapter was part of the Round-Table Conference on prevention of osteoporosis. Please refer to the round-table discussion, page 187.