Panel Session: Prevention/Treatment

Alternative Strategies for Prevention of Postmenopausal Osteoporosis

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Synopsis

Osteoporosis is more readily prevented than treated, and early intervention with effective therapy would be expected to reduce significantly the impact of osteoporotic fractures among the aging population. For the postmenopausal female population, estrogen is the cornerstone of therapy, and multiple studies have demonstrated efficacy in reducing cortical and trabecular bone loss in the axial and peripheral skeleton. Alternative strategies for those who cannot, or will not, take estrogen and who can be documented to be at increased risk of osteoporosis, include calcium supplementation, progestogens, (particularly the 19-nortestosterone derivatives), calcitonin, diphosphonates, and anabolic steroids. All have been shown in some populations to reduce the rate of bone loss to a greater or lesser extent, although, overall, the data are as yet inconclusive. All regimes, with the exception of moderate calcium supplementation, have negative aspects to their use currently, and further research is required before a definitive alternative to estrogen for prevention of postmenopausal osteoporosis can be recommended. Only estrogens and calcitonin have Food and Drug Administration (FDA) approval for use in the treatment of osteoporosis.

In the decision-making process for the woman at mid-life, risk factor assessment, although a poor quantitative tool for the individual patient, is the starting point for the evaluation of patients. Bone mass measurements play a crucial role in assisting the dubious patient (or physician) about the need for therapy.

Estrogen use, however, is a more important issue for the postmenopausal female, with sequelae other than its effects on bone to be considered, including effects on cardiovascular disease, endometrial and breast cancer, which must be considered in the equation of risk-benefit. The greater the risks and costs of the intervention strategies available, the more important effective identification of the target population becomes. Estrogens, however, provide the most effective preventive treatment for osteoporosis. This review will deal primarily with the decision to introduce estrogen treatment, and the efficacy of estrogens, as well as alternative forms of prevention.

FOR MANY DISORDERS of aging in which multiple pathenogenetic factors have been identified, it has become common practice to identify factors that increase risk, as well as those whose presence decreases risk (*1*). Osteoporosis has not escaped this process, and, as interest in the problem has increased, so also has the list of factors that are thought to change fracture risk (table 1). These risk factors could influence the likelihood of fracture in one of several ways. They could alter peak skeletal mass by influencing growth and skeletal maturation, change the rate or duration of the rapid phase of bone loss, or alter the potential for falling, often the immediate stimulus for fractures, especially those of the distal radius and hip. That all risk factors are often grouped indicates our somewhat cloudy thinking about the individual role that they play in the pathogenesis of fracture, as well as the likelihood that several may play important roles at more than one locus on the path to fracture.

Identification of Candidates for Treatment

Quantifying those risk factors that might be expected to influence bone mass at the point of intervention has been attempted, and, perhaps not unexpectedly, met with little success. That such attempts are made at all suggests the importance of bone mass (at, say, menopause) in the minds of investigators as itself an important identifier of those at greatest risk of the disorder. While attractive, the hypothesis that those with low bone mass at meno-

pause will be those most likely to fracture at a later stage in life has not been proved. Presently, knowledge of the age and sex of a normal healthy adult allows prediction of the present bone mass with a standard deviation of 10–15 percent. The use of other risk factors does not improve precision. Thus, identification of the presence of low bone mass requires direct measurement of the skeleton, preferably using a noninvasive technique, at a site of clinical importance, i.e., where fracture is likely to occur.

The physician can, however, also use his or her clinical judgment in identifying those most likely to benefit from prevention therapy. The presence of several risk factors, for example, might indicate that therapy should be considered. In that circumstance, bone mass measurements serve as additional information in the decision-making process. The absence of risk factors probably lowers the likelihood of osteoporosis but does not eliminate it, and when the question of relative risk is raised by an individual patient, it is useful to have both a clinical assessment and a bone mass measurement.

Table 1. Risk factors for osteoporotic fracture

Established	Female gender Increasing age (postmenopausal) Caucasian Bilateral oophorectomy (premature menopause) Low body weight Excess alcohol intake Excess corticosteroids Chronic disabling disorders (e.g., rheumatoid arthritis) Low bone mass Psychotropic drug use Cigarette consumption (?)
Postulated	Family history of osteoporosis Asian race Low calcium intake Sedentary lifestyle Nulliparity Moderate alcohol intake Caffeine intake High protein diet Thyroid supplements Diabetes Type I Scoliosis

Estrogen Therapy

The use of estrogen replacement therapy (ERT) to treat postmenopausal women has reversed from the original concept that all women should be given estrogen, to a rapid decline in its use after identification of the problem of endometrial malignancy. Indeed, that such a side effect should have been found demonstrates the lack of understanding that existed about the physiology of estrogen action and epitomizes the care that must be exercised when any therapeutic agent is widely used.

The administration of ERT reduces the rate of bone loss among estrogen-deprived women (*2*). In our long-term studies we have demonstrated inhibition of peripheral cortical bone loss that is independent of time after ovarian failure and rate of loss of bone (*3–5*). Indeed, effective ERT, when provided during rapid bone loss, produces a small increase in bone mass as the remodeling space within the skeleton is gradually filled by the osteoblast population. The therapy is effective for as long as it is provided (controlled studies now have provided data in excess of 10 years). In addition to the prevention of loss of cortical bone, cross-sectional data have confirmed that bone mass at both vertebral and femoral neck sites is preserved (*6*). We have also demonstrated that vertebral deformity, observed in lateral radiographs in some placebo-treated patients, is significantly less evident in patients given estrogen (*4*). Retrospective and case-control studies confirm that estrogens protect against fractures of vertebral bodies and the femoral neck, with reductions of 50 percent or more in the prevalence of the latter if therapy is begun early (usually defined as within 5 years of menopause) and continued for at least 5 years (*7–10*).

The use of long-term, unopposed, high-dose estrogen therapy produces an exaggeration of endometrial growth, a normal physiological response to estrogens (*11*). If allowed to continue, this hyperplastic response may become malignant. The risk of endometrial malignancy, primarily determined in patients on oral conjugated equine estrogens, appears to be two to eight times that for the normal, untreated postmenopausal population, and constitutes the main risk of estrogen treatment. From a public health standpoint, the number of cancers that can be attributed to estrogen appears to be small, and the likelihood of death as the outcome even smaller. The addition of progestogens to the treatment regimen reduces the likelihood of endometrial hyperplasia and presumably also reduces the chance of malignancy, although the latter has yet to be demonstrated on a population basis. The addition of progestogens does not appear to significantly affect the skeletal effects of estrogen, but may, at least potentially, negate some of the beneficial effects of estrogen on the cardiovascular system, presumed to be consequent upon changes in circulating lipoproteins.

Other side effects of estrogens include an apparent doubling of the risk of gallstones, which is possibly

associated only with the administration of estrogen by the oral route, and an idiosyncratic increase in blood pressure, seen only in unusual cases. The relationship of estrogen therapy to the incidence of breast cancer in the postmenopausal population is not yet established. Most studies that have examined this issue have found no change in breast cancer incidence, or even a modest protective effect. However, some data conflict with these conclusions, showing a small but significant increase in risk. While the role of progestogens in preventing endometrial hyperstimulation seems clear, no such similar role has been confirmed for prevention of breast cancer, although some uncontrolled data suggest that such an effect might be present (*12*). This important issue is worthy of more detailed study.

ERT is not associated with an increased incidence of thromboembolic phenomena, a decline in carbohydrate tolerance, or a general increase in blood pressure. Indeed, our data suggest that a rise in blood pressure in the postmenopausal population is related to increased weight, which seems more likely to occur in women who are not given estrogen treatment (*13*). Other beneficial effects of estrogen have been suggested. Menopausal symptoms are sensitive to the addition of estrogen, with marked relief of hot flashes. Similarly, the gynecological problems that follow menopause are also relieved by estrogens. Vaginal atrophy, resulting in painful intercourse, and urinary incontinence are both symptoms of estrogen deficiency in this population.

Perhaps of maximum importance has been the suggestion that estrogen treatment reduces the incidence of ischemic heart disease in the aging female population. Several case-control and retrospective epidemiologic studies have confirmed this, and only data from the Framingham study do not show an effect (*14*). However, methodological problems in the analysis may have confounded this study. The most convincing data are those from a national nurses' study, which suggested a reduction of 50 percent in coronary incidents in certain estrogen-treated women (*15*). It has been proposed that this dramatic effect results from the changes in lipid metabolism that are induced when estrogens are given to postmenopausal-deficient women. Most studies performed with oral estrogens have found a decline in low-density lipoprotein cholesterol (LDL) and a rise in high-density lipoprotein cholesterol (HDL) levels, particularly the HDL_2 subfraction. These changes would be consistent with protection against ischemic heart disease. However, no data have prospectively linked these two effects. Prospective data on the cardioprotective effects themselves are needed, to eliminate the potential biases inherent in any retrospective study.

The decision regarding the initiation of estrogen treament becomes, therefore, a personal assessment of the benefits and risks of both taking the medication and of not taking it. A woman entering her menopausal years with multiple risk factors for osteoporotic fractures and low bone mass needs to be fully cognizant of the possible outcome of a decision not to take estrogens.

Recognizing the limitations imposed by the data available at the present time, we (the patient and physician) use both risk factor analysis and bone mass measurement in the decision-making process. We also assume that risk factors are both additive and cumulative, but we know that we cannot quantify overall risk, or the contribution of risk factors, for each patient. We allow each patient to make a self-assessment of risk using a simple, self-administered questionnaire. The results and outcomes (risk modification) are discussed with a nurse. Therapeutic options are discussed with a physician. If a patient is in doubt about risk, risk modification requirements, or interventive therapy, a bone mass measurement is obtained. Our preliminary data suggest that bone mass at menopause, which is representative of peak bone mass, is predictive for bone mass in future years. Thus, low bone mass is an indicator for aggressive intervention at this point in a woman's life.

Alternatives

Calcium. The simplest intervention would be ingested calcium, either as a dietary constituent or as a supplement. For the specific postmenopausal population, the data suggest that calcium has a minimal effect on the loss of trabecular bone, but may reduce the rate of loss of cortical bone, although it is generally much less effective than estrogen (*14*). Nonetheless, Heaney's kinetic data (*16*) are sufficiently convincing to recommend a total intake of 1,500 milligrams (mg) per day for all women considered to be at risk of osteoporosis. At that level, we can be reasonably sure that calcium deficiency is not exacerbating the primary cause of osteoporosis, whether that be ovarian insufficiency or adrenal excess. Calcium by itself does not appear to constitute a sufficiently effective treatment for bone-loss prevention at this intake.

Calcitonin. Calcitonin is a 32-amino acid polypeptide synthesized primarily in the C-cells of the thyroid

gland. It is secreted principally in response to an acute increase in serum calcium, and appears to be a specific inhibitor of osteoclast bone resorption, at least in some species. Calcitonin has been used for some years in the treatment of Paget's disease of bone and hypercalcemia of malignancy, often with good response, especially in the former disorder, although complete inhibition of the disordered and excessive bone resorption does not usually occur except in mild cases.

Calcitonin has been used in the treatment of established osteoporosis, mostly in patients with crush fractures. Generally, the introduction of treatment as subcutaneous doses of 50–100 mg per day on alternate days has retarded further loss of bone, and even resulted in an increase in skeletal density (usually 2–10 percent) or in total body calcium (2–5 percent). These results are consistent, and are compatible with inhibition of bone loss in patients who are still experiencing significant rates of bone loss, and a consequent remineralization of the remodeling space. Calcitonin is more effective than calcium alone in this circumstance (*17*). Calcitonin may reduce back pain in patients with crush fractures, although it is difficult to quantify the effect. An analgesic action for calcitonin has been suggested in other situations.

Few data are available for evaluating the effect of calcitonin in prevention of the acceleration of bone loss after menopause. A number of reasons can be given for this. First, calcitonin, as available commercially at present, must be given parenterally and is expensive. Second, the overall effects of calcitonin are inferior to those of estrogen for the newly estrogen-deprived population. Finally, it is becoming difficult to conduct controlled studies of patients in the immediate postmenopausal period, because estrogens have been convincingly shown to be effective both in control of symptoms and also because of the consistent effects of estrogen on bone loss. One preliminary study does, however, suggest that calcitonin can reduce the rate of bone loss in the immediate postmenopausal phase of life. In that controlled study comparing calcitonin with estrogen, J.S. Stevenson demonstrated an effect after 1 year of therapy. There appeared to be a lesser effect of calcitonin during the second year, a result the researcher attributes to poor compliance. The recent development of intranasal calcitonin, provided the drug is sufficiently bioavailable to produce antiresorptive effects, will provide an alternative to parenteral administration that may be acceptable to the asymptomatic patient. Since bioavailability is modest with this route of administration, further efficacy data are needed.

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Diphosphonates. The diphosphonates are synthetic analogues of diphosphates, in which the oxygen atom linking the phosphates is replaced by a carbon atom, making the resulting compound resistant to biological degradation by phosphatase enzymes. Diphosphonates are "bone-seeking" compounds, to a variable extent, and appear to inhibit osteoclastic bone resorption. Available compounds have been used successfully in hypercalcemia of malignancy, and Paget's disease of bone. Data suggest that diphosphonates given intermittently or continuously to patients with established osteoporosis will slow bone loss, or result in an increment in mass equivalent to refilling the remodelling space in patients with established osteoporosis. However, data are lacking on prevention of bone loss in postmenopausal women, although at least one study has been undertaken. The commercially available compound EHDP (the disodium salt of l-hydroxyethylidene diphosphonic acid) may not be the ideal candidate for this purpose, since in high doses it inhibits mineralization and produces histological osteomalacia. Asymptomatic abnormalities of mineralization may also be seen at lower doses in the therapeutic range.

Anabolic steroids. Anabolic steroids have also been shown to reduce bone loss in patients with established osteoporosis. However, their androgenic side effects, including potentially adverse effects on lipoprotein metabolism, render them unsuitable for use as preventive agents.

Progestogens. Some data suggest that both 19-nortestosterone derivatives and C-21 "true" progestogens can reduce the rate of bone loss in postmenopausal women. However, the doses are somewhat large, and these compounds, particularly the 19-nortestosterone derivatives, are often not well tolerated in estrogen-deficient women. Reductions in HDL and increases in LDL also occur with these compounds, the magnitude of the effects being dependent on the dose and androgenicity of the compound. The use of progestogens together with estrogens does not appear to affect significantly the

skeletal response to estrogen. Hybrid compounds may be useful agents, but have been inadequately studied as yet.

Conclusions

Estrogens remain the major therapy for prevention of osteoporosis in postmenopausal women. While other potential candidates for use in prevention of bone loss exist, insufficient data are as yet available on efficacy, compliance, and side effects. Indeed, none of the available compounds has the overall effects of estrogen on the general health of the postmenopausal woman. For the high-risk woman who does not wish to take estrogen treatment, other possible therapies include calcitonin and progestogens, with a recognition of the risk factors.

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Panel Session: Prevention/Treatment

Hormonal Therapy in Climacteric Women: Compliance and Its Socioeconomic Impact

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Synopsis

Hormonal therapy can effectively enhance the quality of life for postmenopausal women, and prevent climacteric-related conditions such as osteoporosis. Since long-term therapy is often required, compliance becomes an important issue. This can best be achieved by measurement, documenting the reason for hormone therapy, and by repeated measurement, demonstrating a response to the treatment. Case histories documenting this principle are described.