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REVIEW

Reasonable osteoporosis prevention: hormone replacement therapy, SERM, or bisphosphonate?*

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Although the objective of osteoporosis prevention in all age groups is to avert the development of bone loss and qualitative bone architecture alterations, the best means of achieving this objective varies according to the age and health status of the patient. In childhood, prevention aims at increasing the peak bone mass. In adults, primary prevention in subjects with normal bone mass or osteopenia seeks to slow the rate of bone loss. Secondary prevention involves increasing bone mineral density in patients who have osteoporosis with or without fractures.

This article discusses only primary prevention in women, particularly after menopause.

PATHOPHYSIOLOGY OF POSTMENOPAUSAL OSTEOPOROSIS

Many studies of bone mineral density have found evidence of rapid bone loss during the three to five years that follow menopause [1, 2]. The rate of bone loss varied across skeletal sites from 3% to 5%. Subsequently, bone loss occurred more slowly, at a rate of 0.5% to 1% per year at all skeletal sites. However, recent longitudinal studies suggest that bone loss increases gradually in very elderly subjects, particularly at the femoral neck.

The bone mass decrease seen after menopause is due to excessive bone resorption relative to bone formation. Biochemical markers for bone remodeling show significant increases, and the markers for resorption increase more than the markers for formation. The levels of bone remodeling markers are negatively correlated with bone mass measured at various skeletal sites. The biochemical markers do not decrease significantly at a distance from the menopause: they are correlated with age, both before and after the menopause. Thus, the role of bone remodeling in determining bone mass increases with age. One cross-sectional and two prospective studies showed recently that biochemical markers for bone remodeling, particularly bone resorption, are useful for evaluating the risk of osteoporotic fractures. The predictive value of these markers is comparable to that of absorptiometry, and combining both methods may allow a more accurate evaluation of the fracture risk.

The sharp increase in bone remodeling seen after menopause results in rapid bone loss, with trabecular breakage and loss resulting in disorganization of the trabecular network. Classically, this rapid bone loss is ascribed to estrogen deprivation, whereas the slower bone loss seen at a distance from the menopause is ascribed to aging (decreased bone formation) and hyperparathyroidism secondary to vitamin D and calcium deficiencies. Very recently, Riggs et al. [3] reported that data from the literature point to estrogen deprivation as the main cause not only of the rapid bone loss seen in the early postmenopausal period but also of the slower bone loss seen later on and of the age-related bone loss seen in men. Estrogens protect the bone tissue via direct effects on cells and bone remodeling and indirect effects on the intestinal absorption and renal excretion of calcium, on vitamin D metabolism, and on parathyroid hormone secretion.

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CURRENT TREATMENTS FOR PREVENTING OSTEOPOROSIS

The objective of osteoporosis prevention is to reduce or stop the bone loss that occurs after menopause. Consequently, treatment efficacy is evaluated based on changes in bone mineral density over time. Three classes of drugs effectively prevent osteoporosis via similar mechanisms: menopausal hormone replacement therapy (HRT), selective estrogen receptor modulators (SERMs), and bisphosphonate. These three classes of drugs slow bone remodeling by inhibiting bone resorption.

Menopausal hormone replacement therapy (HRT)

Estrogen replacement therapy has been proved effective in slowing bone loss after menopause. Epidemiological studies suggest that HRT decreases the incidence of osteoporotic fractures by about 50% [4, 5]. Furthermore, HRT has many other beneficial effects, including partial or complete relief from hot flushes and a reduction in the cardiovascular risk increase seen after the menopause. As a result, HRT is often described as the best preventive treatment for osteoporosis. However, HRT is less than ideal, for several reasons. First, its efficacy has probably been overestimated because women who accept or ask for HRT tend to be in better health than those who do not [5]. Second, the beneficial effect of HRT on the cardiovascular risk is generating considerable debate, which may end only when the results of ongoing controlled trials become available [6]. Third, the Framingham study showed that significant bone stock preservation occurs only when HRT is taken for seven years or more [7], a treatment duration associated in vast epidemiological studies with a significant increase in the risk of breast cancer [8].

Bisphosphonate

The most convincing evidence that bisphosphonates prevent postmenopausal bone loss was obtained with alendronate and risedronate [9-12]. According to the dose used, two to four years of therapy were associated with prevention of bone loss at the femur and lumbar spine and with increases in bone mineral density in women in early menopause. Yet, treatment discontinuation was followed by a rapid increase in bone remodeling and with acceleration of the pace of bone loss, which became comparable to that seen with a placebo [11, 12].

SERMs

In a multicenter, randomized, placebo-controlled study conducted in Europe, raloxifene in a dose of 60 mg per day for two years was effective in preventing lumbar spine, femoral, and whole body bone loss [13]. Under raloxifene, biochemical markers for bone remodeling decreased to the levels seen before the menopause. Raloxifene failed to provide relief from hot flashes and caused a small increase in the risk of venous thrombosis and pulmonary embolism similar in magnitude to that seen with HRT. Raloxifene decreased serum levels of total cholesterol and LDL-cholesterol. The effects of raloxifene on the risk of coronary heart disease are under evaluation.

The MORE study evaluated the efficacy of raloxifene in decreasing the incidence of fractures in women with osteoporosis. A 50% decrease in the incidence of vertebral fractures was found [14]. In addition, the risk of invasive breast cancer decreased by 65% [15]. Raloxifene is currently being evaluated as a means of primary breast cancer prevention in women at high risk for the disease

GENERAL CONSIDERATIONS ON OSTEOPOROSIS PREVENTION AND INDIVIDUAL TREATMENT STRATEGIES

There are two strategies for primary osteoporosis prevention [16]. 'Mass' prevention involves use in the entire population of measures designed to correct identified risk factors for osteoporosis. Examples of such measures include recommending that adolescents and elderly subjects increase their dietary calcium intake, promoting lifelong participation in sports, and discouraging the use of alcohol and cigarettes. These measures are of limited efficacy, for two reasons: they are put into practice by only a small fraction of the population, and the risk factors they target have only a small impact on the incidence of osteoporosis [17]. Consequently, attention has turned to the other strategy, namely, targeted prevention based on detection of high-risk individuals. Because treatment efficacy is far greater in high-risk subjects than in the population at large [17], the yield of targeted prevention is considerably higher than the yield of mass prevention. The costs of these two strategies are related both to the costs of treatment and to the cost of identifying high-risk subjects.

These general considerations explain why the respective places of HRT, SERMs, and bisphosphonates in the preventive treatment of osteoporosis are difficult to

evaluate. HRT and SERMs have major extraskeletal effects that can either support or contraindicate their use. If their beneficial effect on the risk of cardiovascular disease is confirmed, as well as the decreased breast cancer risk with SERM therapy, these treatments will become candidates for use in a mass prevention strategy, in which osteoporosis prevention would be only one of their indications. Conversely, bisphosphonates have proven effects only on bone tissue and consequently can be used only in a targeted strategy involving identification of subjects with a decrease in bone mineral density. The indications for absorptiometry include a family history of osteoporosis, a diet low in calcium since childhood, a history of corticosteroid therapy, and a combination of smoking and low body weight.

During the first few years that follow menopause, HRT is the only treatment that provides relief from hot flashes, which are often the only complaint at this stage. In patients who cannot or do not want to take HRT, raloxifene or bisphosphonate therapy may be indicated if risk factors for osteoporosis are identified and/or if absorptiometry shows a decrease in bone mass. However, although alendronate, risedronate, and raloxifene are approved in France for osteoporosis prevention, they are not reimbursed by the national health insurance system in this indication, and some patients may be unable to pay for them.

The risk of breast cancer associated with HRT is directly related to treatment duration. Intermittent treatment has been suggested as a means of limiting the breast cancer risk. This strategy involves giving HRT during two periods, namely, the first few years after the menopause to relieve climacteric manifestations, then later in life to prevent osteoporotic fractures in high-risk women. However, the cumulative risk of breast cancer associated with intermittent HRT remains unknown. Raloxifene may be particularly useful at a distance from the menopause.

Thus, HRT, alendronate, risedronate, and raloxifene are effective in preventing osteoporosis. Only HRT is reimbursed by the national health insurance system in France. Treatment selection rests on cost considerations; on evaluation in each individual patient of the risk of osteoporosis, cardiovascular disease, and breast cancer; on the results of a search for contraindications to a given drug; and on the wishes expressed by the patient after receiving complete and objective information.

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