

An expanded overview of postmenopausal osteoporosis

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Abstract

Why is the incidence of osteoporotic fracture so much higher in women than in men? The dominant medical view holds that the exaggerated skeletal fragility and fracture risk of postmenopausal women solely reflects the loss of bone following withdrawal of endogenous estrogen. Indeed, an enormous amount of research in this area has attempted to understand the rise in fractures after menopause in terms of the impact of estrogen lack on bone remodeling. Recent insights suggest that this simple view does not offer an adequate explanation for the greater susceptibility of older women to fracture compared to that of men. It seems more reasonable to view bone health as a lifelong process, reflecting the contributions and influences of myriad events occurring throughout life to skeletal acquisition and maintenance. Only recently has the medical community recognized that the amount of bone present at skeletal maturity makes a powerful contribution to lifelong skeletal status. A second area that must be incorporated into discussions of this topic relates to bone size and geometry. Women's bones are inherently smaller than those of men. A bone's strength is determined by its size as well as by its material properties. In boys, pubertal increases in the cortical thickness of long bones are achieved by (testosterone-dependent) periosteal apposition. By contrast, increased cortical thickness in girls reflects bone expansion into the medullary space, with little or no periosteal apposition, suggesting an inhibitory effect of estrogen on the latter process. Consequently, at skeletal maturity, men have wider bones of greater mechanical competence. Although estrogen is generally held to be skeletally protective, this aspect of its actions may actually render women more susceptible to some fractures. In later life, men may lose even more bone from appendicular sites than do women, but men show much greater concomitant increases in periosteal apposition than women, permitting them to maintain a relatively favorable mechanical profile. These several findings are based on cross-sectional observations of relatively few individuals and therefore require confirmation in prospective longitudinal studies. The degree to which gender-related differences in later life skeletal adaptation reflects a bone's mechanical or metabolic environment has been frequently discussed but still awaits experimental confirmation.

Keywords: Menopause, Fracture, Estrogen, Bone Geometry, Therapeutic Advances

The last decade has witnessed enormous progress in our understanding of and ability both to prevent and treat postmenopausal osteoporosis. As this progress has occurred, however, a number of additional questions have emerged. The dominant medical view of this condition has proven overly simplistic and inadequate to explain completely the vulnerability of postmenopausal women to fractures, and even the astonishing successes of antiresorptive therapies has created a spate of new issues regarding their long-term consequences as well as their optimal use. This presentation will summarize current understanding of these various issues.

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The traditional concept of postmenopausal osteoporosis

As first promulgated by Albright, and subsequently expanded greatly by Riggs and colleagues^{1,2}, postmenopausal osteoporosis is viewed as the result of bone loss in response to the loss of endogenous estrogen. That such loss occurs is beyond dispute, and an enormous body of scholarship has made enormous progress in defining the physiologic and molecular processes involved in its genesis. This model of bone loss has become entrenched in the medical community and considerable effort has been spent to develop laboratory approaches to identify women who are potentially "rapid losers", who would therefore be at highest risk to develop osteoporosis. However, it is now clear that models of osteoporosis predicated exclusively on bone loss do not accommodate recent knowledge about the roles of other

features of skeletal status that exert a powerful influence on long-term fracture risk, including for example, the contribution of peak bone mass, gender-specific modeling during pubertal growth, and gender-specific adaptations in bone geometry with age. Only by incorporating these influences into a comprehensive view of skeletal aging can one begin to understand why women in general, and older women, in particular, are most vulnerable to skeletal fragility.

A stochastic view of bone health

Rather than focus entirely on mid- and late life events of bone loss, it seems more appropriate to recognize that skeletal vigor represents the net result of myriad events confronting it throughout life. These include genetic endowment, early life exposures, pubertal bone acquisition, illness and medication history, and age-dependent changes, including those associated with menopause. Although the contributions of many of these are now accepted and reasonably understood by the bone community, two gender-specific issues that are less well understood are of particular interest here; these relate to bone modeling and later-life adaptation. Women's bones are inherently smaller than those of men. A bone's strength is determined by its size as well as by its material properties. In boys, pubertal increases in the cortical thickness of long bones are achieved by (testosterone-dependent) periosteal apposition. By contrast, increased cortical thickness in girls reflects bone expansion into the medullary space, with little or no periosteal apposition, suggesting an inhibitory effect of estrogen on the latter process³. Consequently, at skeletal maturity, men have wider bones of greater mechanical competence. Although estrogen is generally held to be skeletally protective, this aspect of its actions may actually render women more susceptible to some fractures. In later life, men may lose even more bone from appendicular sites than do women, but men show much greater concomitant increases in periosteal apposition than women, permitting them to maintain a relatively favorable mechanical profile (Seeman, personal communication, 2001). These several findings are based on cross-sectional observations of relatively few individuals and therefore require confirmation in prospective longitudinal studies. The degree to which gender-related differences in later life skeletal adaptation reflects a bone's mechanical or metabolic environment has been frequently discussed but still awaits experimental confirmation.

Advances in therapy of postmenopausal osteoporosis

Little more than a decade ago, physicians had nothing to offer their osteoporotic patients beyond standard hygienic measures (calcium, vitamin D) and estrogen replacement therapy. Even for those, no solid evidence base gave assurance that the interventions would reduce fracture risk. We now enjoy the enviable position of being able to select from among several antiresorptive agents that are FDA-

approved for the prevention and treatment of postmenopausal osteoporosis. In addition to estrogen (currently approved for prevention only), these include two potent aminobisphosphonates, a SERM, and salmon calcitonin. In each case, drug efficacy, defined as prevention of fracture, has been established by large randomized controlled trials^{4,8}. For each, evidence indicates that treatment for ~3 years diminishes the rate of new vertebral fracture by ~50%. With respect to non-vertebral (particularly hip) fractures, only the two bisphosphonates, alendronate and risedronate, have shown significant benefit^{4,8}.

Despite this embarrassment of riches, several very important practical questions remain unsettled. These concern the appropriate selection of patients for treatment, optimal duration of therapy, and, as an extension of the previous question, the consequences of drug termination.

Patient selection

The raloxifene and bisphosphonate trials show a reduction in vertebral fracture. The consistent effect size of ~50% depends neither on initial bone density nor on the history of previous fractures prior to initiating therapy. However, evidence clearly shows that the absolute number of fractures that will occur is 4-5 fold greater in women who have already sustained a fracture^{4,5}. Thus, the *number of individuals needed to treat* to prevent a single fracture is substantially greater in a group of osteoporotic women who have not sustained a fracture. This fact has powerful health care and economic consequences and remains a contentious point of contention within the field. At present, there is general agreement that the following older women should be offered treatment:

- Those with low bone mass and a previous fragility fracture.
- Those with bone density T-scores below -2.5.
- By current published guidelines, those with T-scores of -2.0 or below.

The value of treating non-fractured patients with T-scores higher than -2.0 (or even -2.5 according to some authors) remains unsettled. Arguments against such a strategy can be based on economics, very small marginal improvement in absolute numbers of fractures, and a low ratio of benefit to potential toxicity.

Treatment duration

Pivotal studies have clarified many parameters of drug treatment efficacy and toxicity, but have not addressed the consequences of treatment termination. Although bone turnover accelerates rapidly when estrogen is discontinued, some persistence of bone density occurs for at least a couple of years after bisphosphonates are stopped. In addition, it is not clear what the added anti-fracture benefit may be with prolonged therapy. A strong case has been made that much

of the benefit occurs early, within the first 2 years of starting medication, but that fracture rates of active and placebo treatment groups are fairly parallel from then on. Although this issue is not settled, concerns about the very long-term safety of bisphosphonates suggest to some authors the value of stopping treatment after 4 or 5 years. If such an approach is used, there is currently no basis for understanding what would ultimately happen to such patients, and whether re-institution of drugs would be associated with yet another reduction in fracture.

Finally, we now face the (hopefully) imminent availability of recombinantly produced Parathyroid Hormone as a true anabolic therapy for osteoporosis. This agent has shown powerful anti-fracture efficacy after only 20 months of therapy⁹. No information currently permits one to understand how PTH would best be used. Whether it would be given as monotherapy as an alternative to antiresorptive treatment or whether it should be administered in tandem or sequentially with antiresorptive therapies remains untested.

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