Panel Session: Management/Education

Osteoporosis in the Older Woman: A Reappraisal

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Synopsis

Osteoporosis is most acutely experienced by the elderly, yet little research has focused on this problem in this group. Recommendations for osteoporosis prevention and treatment in the elderly have been extrapolated from studies of perimenopausal women. However, there are substantial differences between perimenopausal and elderly women in factors related to bone metabolism, rate of bone loss, architecture of remaining bone, the types of fractures sustained, and risk factors for fracture. Finally, unlike the perimenopausal women, the majority of older women already have osteopenia, or bone loss. Each of these factors is reviewed, and its implications for treatment and future research are explored.

THE FASTEST GROWING SEGMENT of the U.S. population consists of persons older than 70, who experience the ravages of osteoporosis most acutely. Twenty-five percent of women older than 70 have had vertebral fractures, as have 50 percent of 80-year-olds. More than 90 percent of hip fractures occur in women older than 70. By the time a woman reaches 90, she has a 35 percent chance of having suffered a hip fracture—a fracture associated with a three-week hospitalization, a mortality of up to 20 percent, a 25 percent chance of long-term institutionalization, and a less-than-even chance of recovering to the prefracture level of independence. The cost of these fractures exceeds $6 billion annually (*1*).

Despite the considerable prevalence, morbidity, and expense of osteoporosis in the elderly, little research has focused on the problem in this population. Recommendations have been extrapolated from those appropriate for perimenopausal women. However, there are substantial differences between the woman older than 70 and the perimenopausal woman. These differences may be significant enough to make us question the current approach.

Age-related Differences in Factors Related to Osteoporosis

Factors related to bone mineral metabolism differ between older and perimenopausal women. For instance, while serum levels of parathyroid hormone (PTH) are low in perimenopausal women, they are increased in the majority of elderly women (*2*). The increased level is associated with biochemical evidence of increased PTH activity, such as nephrogenous cAMP. Vitamin D metabolism changes with age as well. Most perimenopausal women have ample exposure to sun and dietary sources of vitamin D, and have normal serum concentrations of this hormone; this is not true in the elderly (*3*). Studies of healthy, community-dwelling elderly persons residing even in the sunny American Southwest have demonstrated frank vitamin D deficiency in 15 percent, and subclinical deficiency in a larger percent (*4*). The problem is more marked in nursing home populations, in whom undetectable levels of vitamin D are found in up to one-half of residents (*5*). The ability to activate vitamin D to its active moiety (calcitriol) declines with age (*6*); besides causing osteomalacia, vitamin D deficiency may lead to osteoporosis (*6*). Since vitamin D may contribute to muscle strength, subclinical vitamin D deficiency may promote falls and fractures through an additional mechanism (*7*).

Older women differ further from their perimenopausal peers. First, cortical bone, and probably trabecular bone, is rapidly lost at the time of menopause (*8*). In older women, bone loss probably slows (and may even cease) (*9, 10*), although the data on trabecular bone loss are not conclusive. Second, although bone geometry and structure are fairly normal in perimenopausal women, bone structure in

older women is abnormal. New data from Ruff and Hayes (*11*) demonstrate that elderly women remodel bone insufficiently to compensate for the loss of bone mineral content. Parfitt's work (*12*) demonstrates that trabecular plates not only thin, but in fact become perforated, losing their "connectivity," and cause loss of bone strength.

Finally, risk factors for fracture for older women differ from those for perimenopausal women. Data from Riggs and Melton (*8*) show that a "fracture threshold" can be used to identify perimenopausal women at risk of vertebral fracture, but fails to identify older women at risk of femoral neck fracture. Because 90 percent of hip fractures are preceded by a fall, falling is frequently cited as a major risk for older women. However, while more than one-third of these individuals fall annually (the rate is age-related), less than 5 percent of falls result in a fracture, so even the discriminatory power of "falling" is limited (*1*). Other risk factors for fracture in the older population have been identified, most important of which seem to be psychotropic medications (*13*). Despite this, no study has yet reported how to weigh such factors, has devised or tested a "risk index" to quantitate an individual's risk, or has shown that reversing these factors results in a lower risk of either falls or fracture. Furthermore, the factors that protect the older woman from fracture in more than 95 percent of falls are still unknown. Delayed reflexes, weakened muscles, increased sway, reduced soft tissue padding—all of which are present in elderly but not in perimenopausal women—may contribute to an inability to absorb the energy from a fall, which in turn would result in a fracture. (*14*).

Thus, there are substantial differences between perimenopausal and elderly women in the factors affecting bone mineral metabolism, the rate of bone loss, the architecture of remaining bone, the types of fractures sustained, and risk factors for fracturing. Finally, unlike the perimenopausal woman, the majority of older women already have osteopenia. With this background, we review the therapeutic implications of these differences.

Therapeutic Implications

Few therapeutic studies of osteoporosis have included older subjects. Those that have, generally used stabilization of bone mineral content or density as their end point. Although probably relevant for perimenopausal women, such an end point may be less valuable for elderly women for several reasons. Since bone loss in elderly women has already slowed (or even stopped in some), and since they have already lost a high proportion of bone, agents shown to arrest bone loss in younger women may do little to reduce fracture risk in older women. Similarly, since bone structural integrity or connectivity is impaired in older women, agents that increase bone density without restoring its architecture may do little to actually strengthen it. Given these constraints, we review the use of four widely recommended interventions—calcium, vitamin D, estrogen, and exercise.

While controversy surrounds the usefulness of calcium supplementation for perimenopausal women, few data are available on older women. None has shown that beginning calcium supplements in old age will decrease fracture rate. Of course, calcium supplementation makes theoretical sense: calcium intake in elderly women is low, the ability to adapt to a low calcium intake declines with age, and PTH increases with age. However, there are potential problems with prescribing large doses of calcium for older women. First, high doses of supplemental calcium may decrease bone turnover, limiting the ability to adequately remodel bone and repair microfractures, thereby perhaps increasing the risk of overt fracture.

Second, supplemental calcium is expensive. In 1985, the median annual income for elderly women was $6,300, which places them at the poverty level by government standards (*15*). Using milk to supply the recommended calcium intake of 1,500 milligrams per day, an older woman would expend about one-fifth of her food income to meet this requirement. The cost of calcium must also include the expense of increased fiber intake, because supplemental calcium may exacerbate constipation in this age group.

Third, hypertension is quite common in the elderly. Currently the drug of choice is a thiazide. When a woman taking a thiazide diuretic adds high-dose calcium and vitamin D, she may be at an increased risk of hypercalcemia if she becomes ill. An age-related decline in thirst sensation may increase her likelihood of dehydration and confusion; this may even be life-threatening, especially if she takes digoxin, which is one of the three most prescribed drugs in the United States.

Finally, compliance with medical regimens correlates inversely with the complexity of the regimen. If the older woman adds calcium, whose benefit is unproved, will she stop taking other medications more important to her immediate health? Without data demonstrating calcium's protective effect against fracture, it is difficult to know whether or how much to prescribe.

The data on vitamin D are no clearer, and there is a high prevalence of vitamin D deficiency in the eld-

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erly. Because even older individuals without a deficiency are less able to activate vitamin D to calcitriol, theoretically, vitamin D supplementation should be beneficial. However, empirical data do not support this assumption, since vitamin D increases bone resorption as well as absorption of calcium (*16*). Also, a narrow therapeutic ratio exists for this population. Even in the absence of diuretics, vitamin D toxicity has been documented with doses of only 2,000 IU per day, inadequate to increase calcium absorption in many elderly women (*6*). Supplementation with the active form of vitamin D, calcitriol, has also failed to be of benefit. One study found that it increased the rate of vertebral fractures (*17*), and another found that it increased cortical bone loss (*18*).

The evidence with respect to estrogen shows that treatment of perimenopausal women will prevent future fractures; the protection extends until at least age 70. However, there is little evidence to suggest that a 70-year-old woman will benefit from newly prescribed estrogen. Two nonrandomized prospective studies have examined the question. The first showed no benefit of estrogen (*19*), while the second showed that bone loss was arrested after a year (*18*). However, even if bone loss were arrested and the effect was maintained, it is unclear whether this effect would be sufficient to prevent fractures.

The protective effect of estrogen against cardiovascular disease is another frequently cited benefit. When estrogen is given to perimenopausal women, the benefit seems real and sustained until at least age 70. From a public health standpoint, the cardiovascular benefit may far outweigh estrogen's protective effect on the skeleton. However, it is difficult to know whether this beneficial effect applies to the 70-year-old woman for whom estrogen is being newly prescribed. The Framingham study (*20*) is the only large study that prospectively examined morbidity related to estrogen use in older women; a twofold increase in cerebrovascular morbidity, and an increase in myocardial infarction among smokers, was found; no change in mortality could be discerned. It is difficult to advocate prophylactic use of estrogen for older women at present, given the likelihood that menses will recur, gynecologic surveillance and periodic endometrial sampling will be necessary, and there will be an increased risk of endometrial cancer.

The rationale seems sound with respect to exercise. Unfortunately, there are few data to support its use for older women, and no study has shown that it will prevent fractures. One study that prescribed exercise for older women revealed that forearm bone mineral content was increased after three years in the two-thirds of the women who could continue exercising (*21*). Whether bone mineral content would increase at other sites, or be protective, remains unknown. There are clearly other benefits of exercise, especially for the elderly, but exercise is potentially a two-edged sword for the skeleton. The sedentary older woman who suddenly becomes active may increase her exposure to accidents and subsequent fractures and, especially if she has subclinical osteoporosis and exercises inappropriately (for instance, she performs anterior flexion exercises), she may actually increase her risk of fracture.

Thus, there is reason to question the validity of extrapolating data derived from perimenopausal women to formulate treatment recommendations for older women. Because most current recommendations are directed toward slowing or arresting bone loss, they may be of limited utility in a population whose bone loss has already slowed, and whose remaining bone is insufficient to withstand trauma. The use of changes in bone mineral content or density as treatment end points may be inappropriate for the older population.

Today, it is unclear that any treatment will prevent fractures in older women by affecting bone density. However, it is still reasonable to advise the older woman to take a multivitamin or two a day, and an adequate amount of calcium. Judiciously designed exercise programs, which take the individual into account, are reasonable, and have benefits other than improving or maintaining the skeletal integrity, especially if they improve postural stability, agility, and the ability to avoid fracture. There is no compelling evidence that estrogen will be beneficial in this population, but the issue is not closed.

Until better treatment is available, however, the most effective strategy remains to do all one can to reduce the risk of falls. The list includes reviewing patients' medications, discontinuing them when feasible; changing to shorter-acting agents with fewer adverse effects on cognition, balance, and blood pressure; helping to correct reversible sensory loss (such as visual problems); treating medical conditions (such as heart failure, peripheral edema, Parkinson's disease, B12 deficiency, foot problems,

and postprandial hypotension); and educating patients about the hazards that permeate the environment, such as throw rugs, cords, slippery stairs, poorly lit stairways, and high-heeled shoes.

Implications for Future Research

We need to know how to identify the older individual who is still losing bone, and how to arrest this loss; we also need to know if treatment will make any difference. We need to learn how to make new and structurally useful bone. We need to determine how to identify the woman at risk of a fracture and, equally important, we need to identify factors that could help to protect women from fractures in more than 95 percent of falls. We need to conduct intervention trials to see if we can reduce the risk. The role of vitamin D deficiency needs to be ascertained, and its role in muscle strength further explored. The role of exercise in preventing fracture, not only by increasing bone mass, but also by increasing muscle strength and agility, needs to be further investigated.

We need to use fractures, not changes in bone mineral content, as our standard. While this is admittedly difficult, such trials are feasible, and anything less may lead to erroneous conclusions that subject older women to needless medication, morbidity, and expense. In terms of bone mass, "the horse is out of the barn," and at present little can be done to restore it. However, it does not necessarily follow that prevention is futile—we just need to think of prevention in a wider context than bone loss. Until effective treatment is developed, we must think in terms of how to prevent fractures in a population that is already osteopenic. That is the challenge. Nearly 15 million women await the answer. It may not be easy, but the current and growing magnitude of the problem demands our immediate attention.

References

1. Cummings, S.R., Kelsey, J.L., Nevitt, M.C., and O'Dowd, K.J.: Epidemiology of osteoporosis and osteoporotic fractures. Epidemiol Rev 7: 178–202 (1985).
2. Marcus, R., Madvig, P., and Young, G.: Age-related changes in parathyroid hormone and parathyroid hormone action in normal humans. J Clin Endocrinol Metab 58: 223–230 (1984).
3. Holick, M.F.: Vitamin D requirements for the elderly. Clin Nutr 5 121–129 (1986).
4. Omdahl, J.L., et al.: Nutritional status in a healthy elderly population: vitamin D. Am J Clin Nutr 36: 1225–1233 (1982).
5. Egsmose, C., et al.: Low serum levels of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in institutionalized old people: influence of solar exposure and vitamin D supplementation. Age Ageing 16: 35–40 (1987).
6. Parfitt, A.M., et al.: Vitamin D and bone health in the elderly. Am J Clin Nutr 36: 1014–1031 (1982).
7. Boland, R.: Role of vitamin D in skeletal muscle function. Endocrinol Rev 7: 434–448 (1986).
8. Riggs, B.L., and Melton, L.J., III: Involutional osteoporosis. N Engl J Med 314: 1676–1686 (1986).
9. Hui, S.L., Wiske, P.S., Norton, J.A., and Johnston, C.C., Jr.: A prospective study of change in bone mass with age in postmenopausal women. J Chronic Dis 35: 715–725 (1982).
10. Riggs, B.L, et al.: Rates of bone loss in the appendicular and axial skeletons of women. J Clin Invest 77: 1487–1491 (1986).
11. Ruff, C.B., and Hayes, W.C.: Sex differences in age-related remodeling of the femur and tibia. J Orthop Res. In press (1988).
12. Parfitt, A.M.: Trabecular bone architecture in the pathogenesis and prevention of fracture. Am J Med 82 (Suppl. 1B): 68–72 (1987).
13. Ray, W.A., et al.: Psychotropic drug use and the risk of hip fracture. N Engl J Med 316: 363–369 (1987).
14. Melton, L.J., III, and Riggs, B.L.: Risk factors for injury after a fall. Clin Geriatr Med 1: 525–538 (1985).
15. Fowles, D.G.: A profile of older Americans: 1986, No. PF3049 (1086)-D996. American Association of Retired Persons, Washington, DC, 1986.
16. Slovik, D.M.: The vitamin D endocrine system, calcium metabolism, and osteoporosis. Spec Top Endocrinol Metab 5: 83–148 (1983).
17. Jenson, G.F., Meinecke, B., Boesen, J., and Transbol, I.: Does 1,25 $(OH)_2D_3$ accelerate spinal bone loss? Clin Orthop Relat Res 192: 215–221 (1985).
18. Jensen, G.F., Christiansen, C., and Transbol, I.: Treatment of postmenopausal osteoporosis. A controlled therapeutic trial comparing oestrogen/gestagen, 1,25-dihydroxy-vitamin D_3 and calcium. Clin Endocrinol 16: 515–524 (1982).
19. Quigley, M.E.T., Martin, P.L., Burnier, A.M., and Brooks, P.: Estrogen therapy arrests bone loss in elderly women. Am J Obstet Gynecol 156: 1516–1523 (1987).
20. Wilson, P.W.F., Garrison, R.J., and Castelli, W.P.: Postmenopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50. N Engl J Med 313: 1038–1043 (1985).
21. Smith, E.L., Jr., Reddan, W., and Smith, P.E.: Physical activity and calcium modalities for bone mineral increase in aged women. Med Sci Sports Exerc 13: 60–64 (1981).