



Some thoughts on osteoporosis in women

ANGELO A. LICATA, MD, PHD

■ Osteoporosis is a debilitating disease of the elderly that has an enormous impact on health costs. New thoughts about pathophysiology are emerging. Age-related changes in skeletal metabolism and hormonal alterations and changes in lifestyle patterns present an array of risk factors. Many regimens are available to treat established disease. Most programs are aimed at preventing further mineral loss. Experimental therapies are directed toward stimulating bone growth. Prevention is the key to treating disease.

□ INDEX TERM: OSTEOPOROSIS □ CLEVE CLIN J MED 1988; 55:233-238

OSTEOPOROSIS is the most common metabolic bone disease of humanity. Its cause is multifactorial. The major etiological components are diet, hormonal factors, and lifestyle patterns. In most patients, inheritance, concurrent diseases, and drugs play a minor role. The disease has a long latent period that produces no symptoms or radiological changes until skeletal loss is irreversible. However, the new techniques of bone densitometry detect calcium loss early and monitor treatment objectively. Prevention, rather than treatment, is advocated today.

For established disease, however, there is no universally accepted treatment. Numerous regimens are used to prevent further skeletal loss. These include calcium, estrogen, vitamins, exercise, calcitonin, and fluoride.^{1,2} Newer treatments that stimulate new bone growth are being studied. This paper reviews all these modalities.

The annual cost attributable to osteoporosis is over 6 billion dollars for acute and convalescent care.³ Over a million fractures occur yearly. About 40% of these are vertebral, 20% femoral, 15% distal forearm, and the remainder are of other skeletal sites. In general, there is a higher incidence of vertebral and Colles (distal fore-

arm) fractures in the immediate postmenopausal years. The latter type reaches peak incidence in the sixth decade, whereas the former continues to increase with age. For femoral fractures, the incidence slowly increases with age but rises exponentially in late life. This fracture is fatal in approximately 10-20% of patients and accounts for most of the rehabilitative cost in those who survive.

From the pathological viewpoint, this disease decreases the amount of normal bone to the point where minor trauma or routine activity produces fractures of the spine, hips, ribs, or wrists. Two forms of this disorder are postulated based upon the type of fracture.⁴ One type arises in the postmenopausal years from a deficiency of estrogen. Bones with high trabecular content, such as vertebrae and wrists, are affected because these are sensitive to estrogen levels. Decreased parathyroid function, calcium absorption, and vitamin D metabolism also occur. The other type of fracture usually occurs later in life and is attributable to aging. However, one cannot discount the late effects of early postmenopausal hormonal deficiency and diet and lifestyle (e.g., exercise) habits even earlier in life. Bone loss is trabecular and cortical, and affects the hip and spine. Compensatory hyperparathyroidism is found, associated with decreased vitamin D production and calcium absorption.

It has been estimated that, over a lifetime, a woman

Department of Endocrinology, The Cleveland Clinic Foundation.
Submitted for publication March 1987; accepted Sep 1987.

loses about 35% of the cortical and 50% of the trabecular bone mass. An age-related component begins between the third and fourth decade and accounts for a yearly loss of 0.3–0.5%. Menopause accelerates this loss to 2–3% annually.⁸ But later there is a return to the rate of loss associated with aging, 0.3–0.5%. Recent studies indicate that skeletal loss may even occur before menopause due to relative lack of estrogen that is not evident from altered menstrual patterns.⁹

CAUSES OF SKELETAL LOSS

The age-dependent loss of bone is due to impaired osteoblastic function.¹⁰ In youth, the forces of formation and resorption are tightly coupled so that bone mass is conserved. With aging, an uncoupling results in less formation for a given degree of resorption. This decreased osteoblastic function is selective, since repair of skeletal fractures is not altered.¹⁰

Other physiological changes of aging compound this process. Calcium absorption is impaired.¹¹ Some studies show decreased formation of vitamin D due to lack of estrogen.^{12,13} Others, but not all, find an insensitivity to parathyroid hormone.^{14,15} There follows a secondary state of hyperparathyroidism that might augment the overall bone loss.^{16,17} Although calcitonin secretion decreases with age, it is unclear what role calcitonin plays.^{18,19} Data show that calcitonin deficiency in thyroidectomized patients is associated with decreased mineral density.²⁰ By inference, such deficiency may aggravate osteoporosis.

Diet may contribute to skeletal loss. Calcium deficiency has been considered a major factor in the past and has become a focus of renewed interest.²¹ The NIH consensus development panel on osteoporosis discussed this in its recommendations.³ If poor nutritional habits develop in youth, a lifelong deficiency of calcium would produce a less than maximally calcified skeleton to withstand the negative effects of aging. This lack of maximal skeletal strength would lead to signs of osteoporosis at an early age.

Other nutritional factors have also been implicated in skeletal loss. Two major issues are a decreased calcium/phosphate ratio (i.e., increased dietary phosphorus) and increased intake of protein. Data in the veterinary literature show that a high-phosphate diet can promote osteoporosis in certain animal species.^{22–26} In humans, however, this is not easily demonstrated.²⁷ Moreover, phosphate depletion may aggravate skeletal loss in some cases.²⁸ Epidemiological data suggest that a lifelong high-

protein diet might lead to osteopenia.^{29,30} Some experimental studies in humans, but not all, show that increased dietary protein promotes hypercalciuria and, secondarily, a negative calcium balance.^{31–33} The contribution of these factors to osteoporosis is unclear. In young experimental animals, these diets promote abnormal osteogenesis.³⁴

A lack of weight-bearing activity negatively affects calcium balance. The hallmark of this phenomenon is the mineral loss associated with space flight.³⁵ To what extent a lifetime of physical inactivity alters the skeleton in later life is not understood. Short-term studies show that physical activity increases bone density by a small percentage.^{36,37} Presumably, this may alter the progression of osteoporosis. Some of the beneficial effects may be due to strengthening of back muscles.³⁸ On the other hand, excessive exercise (i.e., long-distance running) in young women may cause low mineral density due to altered menstrual function and estrogen status.^{39,40} Running over 40 miles per week is associated with these problems, whereas running less than 25 miles per week is not.³⁹ However, this issue is more complex than initially realized since abnormal secretory dynamics of gonadotropins, and not intensity of exercise, may be the critical factor.⁴⁰ In contrast, older people (i.e., 50–72 years of age) benefit from intense exercise, such as running 25 miles weekly.⁴¹

Other risk factors include overuse of tobacco, alcohol, and caffeine. Alcohol abuse leads to skeletal disease of varying histomorphometry.⁴² In some alcoholic subjects with gastric resection, there is an abundance of osteoid and osteoclasts. In others, typical osteoporosis is found.⁴³ Routine serum chemical values and vitamin D levels are normal.⁴² There is a mild increase in parathyroid activity as assessed from cyclic AMP measurements and PTH measurements.⁴² Alcohol-induced cortisol excess may also contribute to skeletal loss.^{44,45}

Epidemiological and experimental data show that women who smoke cigarettes have an earlier menopause, a higher incidence of vertebral compression fractures, increased loss of metacarpal cortical bone, and a lower urinary estrogen level.^{46,47} Women who smoke an average of 12 cigarettes a day have a lower serum estrogen, even when taking oral supplements.⁴⁸ If the effect on endogenously produced estrogens is similar, then the abnormal menstrual patterns and bone loss are readily understandable.

Caffeine may have a negative effect on bone metabolism, but the data must be accepted with some reservation. Metabolic balance studies show that small amounts of caffeine (i.e., two cups of coffee per day) cause a net

daily loss of 6.0 mg of calcium.⁴⁹ It is inferred that larger quantities may produce losses of 40 mg or more daily that could eventually produce the skeletal losses seen in osteoporosis. However, to extrapolate these data to levels of caffeine intake consumed in more than 10 cups a day (85 mg of caffeine per cup) may not be truly warranted in light of experimental studies in rats.⁵⁰ The deleterious effect of chronic administration of large doses of caffeine on calcium balance in experimental rats was not evident so long as the animals were able to increase calcium absorption. This increase in efficiency is directly related to an increase in the production of vitamin D. The caveat, however, is that the older animals that have impaired vitamin D production may be deleteriously affected by caffeine. This has not been studied in human subjects.

BONE DENSITOMETRY

More than 30% of skeletal calcium must be lost before it is discernible on a routine radiograph. Hence, the disease progresses relentlessly for years until it produces clinical symptoms. With the advent of bone densitometry, it is possible to detect osteopenia many years before it becomes clinically or radiologically evident.

The major forms of densitometry are single (SPA) and dual-photon absorptiometry (DPA) and quantitative computed tomographic (QCT) scanning. Each has unique advantages and disadvantages.

Single-photon absorptiometry was the earliest technique developed to measure skeletal "density." It does not measure a true density but an areal (two-dimensional) value. It quantitates mineral in the distal forearm where cortical bone predominates, is associated with minimal radiation exposure (i.e., about 5×10^{-6} Gy per scan), is useful for mass screening, and has excellent precision. Its major drawback is that it measures calcium in an anatomical region that does not correlate well with the early trabecular bone loss in the hip and vertebrae.⁵¹ Hence, SPA will not detect the early stages of postmenopausal osteoporosis.

Dual-photon absorptiometry (DPA) measures skeletal density in the lumbar and femoral neck areas where trabecular bone loss is greatest.^{52,53} This technique also quantitates a two-dimensional value because it does not measure depth. Radiation exposure is about $1.0\text{--}1.5 \times 10^{-5}$ Gy. Results are spuriously elevated by compression fractures and extrasosseous calcifications. However, it can detect early loss of trabecular bone in osteoporotic patients even when SPA measurements are normal.

QCT scanning measures cubic density of bone in the vertebrae.^{53,54} Radiation exposure ranges from 1–10 Gy depending on the scanner and radiation source (i.e., single versus dual energy). Measurements are influenced by factors attributable to the physics of the machinery, programing techniques, and body fat.^{54,55}

Despite these advances, there are many concerns about the inappropriate use of this equipment and the financial burdens it may impose on the health care system.⁵⁶ Charges for densitometry vary considerably. SPA ranges from \$35 to \$120 per scan, DPA \$100 to \$300, and QCT \$100 to \$350.⁵⁷ The initial investment in the SPA equipment is about \$10,000 to \$25,000, with an added cost of \$800 to \$1,600 every four to six months for the isotopic source. The DPA instruments cost \$30,000 to \$70,000 and use an isotopic source that costs \$7,000 every $1\frac{1}{2}$ years. QCT measurements can be performed on existing CT scanners after modifying software appropriately and using skeletal standards called phantoms. Generally, these cost \$5,000 to \$15,000. The initial investment in the scanner, however, is \$300,000 to \$1,200,000.⁵⁸

The major question, however, is whether these measurements can ascertain which patients are at risk for fracture. At present, the data help assess risk of fracture in large populations but do not accurately predict the risk in an individual. This may be because these techniques do not assess all qualitative aspects of bone that provide strength.⁵⁹ Since the predictive value of a measurement is at present not very good, mass screening of women is not an ideal use of these instruments. The instruments are best used to ascertain the mineral content in high-risk patients and monitor the effect of therapy that may be either expensive or potentially toxic.⁵⁸ Finally, it should be kept in mind that longitudinal measurements performed over short periods (i.e., months) in the same patient may not be accurate, since the skeletal loss is less than the error in measurement.⁶⁰

TREATMENT

Osteoporosis is not treated effectively once the disease is clinically present. Prevention is an important issue for the younger individual, while specific treatment to prevent pain and stop further bone loss is important in the older patient.

The younger patient with minimal osteopenia and no symptoms of osteoporosis is a major focus of all present-day programs. The more bone mass present at a younger age, the greater the probability that prevention will

maintain this skeletal mass into later life. A nutritious diet with at least a gram of elemental calcium per day and daily exercise is paramount to maintain overall skeletal health. Use of estrogen at menopause is the best protective treatment known.⁶¹⁻⁶³ The relationship between estrogen and endometrial and breast cancers is still being discussed.⁶⁴⁻⁶⁸ Recent studies indicate acceptable risk for the use of this drug and even emphasize an enhanced quality of life that exceeds the benefits to the skeleton alone.⁶⁹ Concurrent use of progestins reduces the risk of endometrial cancer, but the best formulation and dose is unclear.⁷⁰⁻⁷² The usual dose of estrogen is 0.625 mg per day given for 25 days and for the last 10 days of the cycle, 10 mg of medroxyprogesterone or 2.5–5.0 mg norethindrone given concurrently with estrogen. A number of side effects may occur, such as withdrawal bleeding, breast tenderness, and premenstrual tension. Menstrual bleeding is much less than that noted in the reproductive years. By age 65, about 40% or more of women will have no cyclic withdrawal bleeding, in spite of no change in the hormonal dosage. Any bleeding during the hormonal cycle, however, must be investigated.

The best treatment in the elderly patient with established disease is still a problem. Although estrogen has a protective effect in early menopause and may be helpful in later life, markedly osteopenic bones need more than protection; they must be strengthened. To do this, several regimens have been used.

In combination with calcium and estrogen, sodium fluoride in doses of 40–60 mg/d increases skeletal density and markedly decreases fracture.⁷³ The drug is still considered experimental and is undergoing clinical trials. It is not clear how to select patients for this treatment. About 40% of patients do not show a response.⁷⁴ Supplemental calcium, and perhaps vitamin D, is needed daily to prevent fluoride-induced osteomalacia.⁷⁵ Significant side effects include nausea, vomiting, fasciitis, anemia, and stress fractures.⁷⁶ A new preparation may prevent some of the gastrointestinal problems.⁷⁷

Supplemental calcium should be given all women to ensure that the total daily dietary intake is 1.0–1.5 g.

Calcium alone is ineffective to suppress trabecular loss in early postmenopausal women, but it does limit cortical loss in older women. Fears about development of renal stones have not been substantiated. Monitoring urinary calcium before and during treatment will prevent problems.

Calcitonin is an injectable hormone used to treat osteoporosis. Calcitonin used with calcium can have an antiosteoclastic effect and can build up skeletal density, but it is not clear how long this increased density persists or whether fracture rate is decreased.⁷⁸⁻⁸⁰ Doses of 100 units every other day may be used.⁸⁰ There may be an analgesic effect in addition to the effect on bone.⁸¹ The inconvenience of administration and the cost limit its use.

Androgenic steroids have also been used to treat osteoporosis.⁸²⁻⁸⁴ Side effects limit their use, however.

The most promising experimental approach to stimulate new bone growth is called *coherence therapy*.⁸⁵ This technique uses sequential application of drugs to stimulate skeletal metabolism, turn down resorption, and allow formation to proceed, thereby depositing a quantum of new bone. Repeated cycles gradually increase skeletal density. Stimulators of bone are phosphate or parathyroid hormone.⁸⁶⁻⁸⁸ Antiosteoclastic agents like calcitonin or the diphosphonates are then used. Thereafter, calcium and/or vitamin D is used to calcify the newly formed bone. Bone biopsies show a variable increase in trabecular volume. Reported mean changes are 36%⁸⁷ and 114%.⁸⁶ Density changes in trabecular bone average 98%.⁸⁸ Although these are promising approaches, it is unclear whether the new bone formed has normal resiliency and strength, whether fracture frequency will be altered, or whether this new bone will persist following treatment.

ANGELO A. LICATA, MD, PHD
Department of Endocrinology
The Cleveland Clinic Foundation
One Clinic Center
9500 Euclid Avenue
Cleveland, Ohio 44195

REFERENCES

1. Riggs BL, Melton LJ III. Involutional osteoporosis. *N Engl J Med* 1986; **314**:1676–1686.
2. Riggs BL, Melton J. Osteoporosis: Current Concepts. Report of the Seventh Ross Conference on Medical Research. Columbus, OH, Ross Laboratories, 1987.
3. Peck WA, Barrett-Connor E, Buckwalter JA, et al. Osteoporosis—Consensus Conference. *JAMA* 1984; **252**:799–802.
4. Riggs BL, Melton LJ III. Evidence for two distinct syndromes of involutional osteoporosis. *Am J Med* 1983; **75**:899–901.
5. Mazess RB. On aging bone loss. *Clin Orthop* 1982; **165**:239–252.
6. Smith DM, Khairi MRA, Johnston CC Jr. The loss of bone mineral with aging and its relationship to risk of fracture. *J Clin Invest* 1975; **56**:311–318.
7. Riggs BL, Wahner HW, Dunn WL, Mazess RB, Offord KP, Melton LJ III. Differential changes of bone mineral density of the appendicular and axial skeleton on aging: relationship to spinal osteoporosis. *J Clin Invest* 1981; **67**:228–235.

8. Riggs BL, Wahner HW, Melton LJ III, Richelson LS, Judd HL, Offord K. Rates of bone loss in the appendicular and axial skeletons of women. Evidence of substantial vertebral bone loss before menopause. *J Clin Invest* 1986; 77:1487-1491.
9. Johnston CC Jr, Hui SL, Witt RM, Appledorn R, Baker RS, Longcope C. Early menopausal changes in bone mass and sex steroids. *J Clin Endocrinol Metab* 1985; 61:905-911.
10. Parfitt AM, Matthews CHE, Villaneuva AR, Kleerekoper M, Frame B, Rao DS. Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the microanatomic and cellular mechanisms of bone loss. *J Clin Invest* 1983; 72:1396-1409.
11. Alevizaki CC, Ikko DG, Singhelakis P. Progressive decrease of true intestinal calcium absorption with age in normal man. *J Nucl Med* 1973; 14:760-762.
12. Buchanan JR, Santen R, Cauffman S, Cavaliere A, Greer RB, Demers LM. The effect of endogenous estrogen fluctuation on metabolism of 25-hydroxyvitamin D. *Calcif Tissue Int* 1986; 39:139-144.
13. Lund BJ, Sorensen OH, Lund BI, Agner E. Serum 1,25-dihydroxy vitamin D in normal subjects and in patients with postmenopausal osteopenia. Influence of age, renal function and oestrogen therapy. *Horm Metab Res* 1982; 14:271-274.
14. Slovik DM, Adams JS, Neer RM, Holick MF, Potts JT Jr. Deficient production of 1,25-dihydroxyvitamin D in elderly osteoporotic patients. *N Engl J Med* 1981; 305:372-374.
15. Riggs BL, Hamstra A, DeLuca HF. Assessment of 25-hydroxyvitamin D 1 α -hydroxylase reserve in postmenopausal osteoporosis by administration of parathyroid extract. *J Clin Endocrinol Metab* 1981; 53:833-835.
16. Wisse PS, Epstein S, Bell NH, Queener SF, Edmondson J, Johnston CC Jr. Increases in immunoreactive parathyroid hormone with age. *N Engl J Med* 1979; 300:1419-1421.
17. Licata AA, Gupta MK. Urinary cyclic adenosine monophosphate discriminates subsets of patients with osteoporosis. *Cleve Clin Q* 1986; 53:345-349.
18. Deftos LJ, Weisman MH, Williams GW, et al. Influence of age and sex on plasma calcitonin in human beings. *N Engl J Med* 1980; 302:1351-1353.
19. Ties RD, Body JJ, Barta JM, Heath H III. Secretion and metabolism of monomeric human calcitonin: effects of age, sex, and thyroid damage. *J Bone Mineral Res* 1986; 1:339-349.
20. McDermott MT, Kidd GS, Blue P, Ghaed V, Hofeldt FD. Reduced bone mineral content in totally thyroidectomized patients: possible effect of calcitonin deficiency. *J Clin Endocrinol Metab* 1983; 56:936-939.
21. Avioli LV. Calcium and osteoporosis. *Annu Rev Nutr* 1984; 4:471-491.
22. Krishnarao GVG, Draper HH. Influence of dietary phosphate on bone resorption in senescent mice. *J Nutr* 1972; 102:1143-1145.
23. Laflamme GH, Jowsey J. Bone and soft tissue changes with oral phosphate supplements. *J Clin Invest* 1972; 51:2834-2840.
24. Schryver HF, Hintz HF, Craig PH. Calcium metabolism in ponies fed a high phosphorus diet. *J Nutr* 1971; 101:259-264.
25. Andersen GH, Draper HH. Effect of dietary phosphorus on calcium metabolism in intact and parathyroidectomized adult rats. *J Nutr* 1972; 102:1123-1132.
26. Draper HH, Sie TL, Bergan JG. Osteoporosis in aging rats induced by high phosphorus diets. *J Nutr* 1972; 102:1133-1142.
27. Zemel MB, Linkswiler HM. Calcium metabolism in the young adult male as affected by level and form of phosphorus intake and level of calcium intake. *J Nutr* 1981; 111:315-324.
28. Dominguez JH, Gray RW, Lemann Jr. Dietary phosphate deprivation in women and men: effects on mineral and acid balances, parathyroid hormone and the metabolism of 25-OH-vitamin D. *J Clin Endocrinol Metab* 1976; 43:1056-1068.
29. Marsh AG, Sanchez TV, Chaffee FL, Mayor GH, Mickelson O. Bone mineral mass in adult lacto-ovo-vegetarian and omnivorous males. *Am J Nutr* 1983; 37:453-456.
30. Mazess RB, Mather W. Bone mineral content of North Alaskan Eskimos. *Am J Clin Nutr* 1974; 27:916-925.
31. Licata AA, Bou E, Bartter FC, West F. Acute effects of dietary protein on calcium metabolism in patient with osteoporosis. *J Gerontol* 1979; 36:14-19.
32. Allen LH, Oddoye EA, Margen S. Protein-induced hypercalciuria: a longer-term study. *Am J Clin Nutr* 1979; 32:741-749.
33. Spencer H, Kramer L, Osis D, Norris C. Effect of a high protein (meat) intake on calcium metabolism in man. *Am J Clin Nutr* 1978; 31:2167-2180.
34. Weiss RE, Gorn A, Dux S, Nimni ME. Influence of high protein diets on cartilage and bone formation in rats. *J Nutr* 1981; 111:804-816.
35. Mack PB, LaChance PA, Vose GP, Vogt FB. Bone demineralization of foot and hand of Gemini-Titan 4, 5 and 7 astronauts during orbital flight. *Am J Roentgenol Radium Ther* 1967; 100:503-511.
36. Aloia JF, Cohn SH, Ostuni JA, Cane R, Ellis K. Prevention of involutional bone loss by exercise. *Ann Intern Med* 1978; 89:356-358.
37. Krølner B, Toft B, Nielsen SP, Tøndevold E. Physical exercise as prophylaxis against involutional vertebral bone loss: a controlled trial. *Clin Sci* 1983; 64:541-546.
38. Sinaki M, McPhee MC, Hodgson SF, Offord KP. Relationship between bone mineral density of spine and strength of back extensors in healthy postmenopausal women. *Mayo Clinic Proc* 1986; 61:116-122.
39. Drinkwater BL, Nilson K, Chestnut CH III, Bremner WJ, Shainholtz S. Bone mineral content of amenorrheic and eumenorrheic athletes. *N Engl J Med* 1984; 311:277-281.
40. Fisher EC, Nelson ME, Frontera WR, Turksoy RN, Evans WJ. Bone mineral content and levels of gonadotropins and estrogens in amenorrheic running women. *J Clin Endocrinol Metab* 1986; 62:1232-1236.
41. Lane NE, Bloch DA, Jones HH, Marshall WH, Wood PD, Fries JF. Long-distance running, bone density, and osteoarthritis. *JAMA* 1986; 255:1147-1151.
42. Bilke DD, Genant HK, Cann C, Pecker RR, Halloran BP, Strewler GJ. Bone disease in alcohol abuse. *Ann Int Med* 1985; 103:42-48.
43. Johnell O, Nilsson BE, Wiklund PE. Bone morphometry in alcoholics. *Clin Orthop* 1982; 165:253-258.
44. Rico H, Gomez-Castresana F, Cabranes JA, Almoguera I, Duran LL, Matute JA. Increased blood cortisol in alcoholic patients with aseptic necrosis of the femoral head. *Calcif Tissue Int* 1985; 37:585-587.
45. Mendelson JH, Ogata M, Mello NK. Adrenal function and alcoholism. I. Serum cortisol. *Psychosomatic Medicine* 1971; 33:145-157.
46. Daniell HW. Osteoporosis of the slender smoker. Vertebral compression fractures and loss of metacarpal cortex in relation to postmenopausal cigarette smoking and lack of obesity. *Arch Intern Med* 1976; 136:298-304.
47. MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette smoking and urinary estrogens. *N Engl J Med* 1982; 307:1062-1065.
48. Jensen J, Christiansen C, Rødbro P. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. *N Engl J Med* 1985; 313:973-975.
49. Heaney RP, Recker RR. Effects of nitrogen, phosphorus, and caffeine on calcium balance in women. *J Lab Clin Med* 1982; 99:46-55.
50. Yeh JK, Aloia JF. Differential effect of caffeine administration on calcium and vitamin D metabolism in young and adult rats. *J Bone Mineral Res* 1986; 1:251-258.
51. Riggs BL, Wahner HW, Dunn WL, Mazess RB, Offord KP. Differential changes in bone mineral density of the appendicular and axial skeleton with aging. Relationship to spinal osteoporosis. *J Clin Invest* 1981; 67:328-335.
52. Wahner HW, Dunn WL, Mazess RB, et al. Dual photon Gd-153 absorptiometry of bone. *Radiology* 1985; 156:203-206.
53. Wahner HW, Dunn WL, Riggs BL. Assessment of bone mineral. Part 2. *J Nucl Med* 1984; 25:1241-1253.
54. Adams JE, Chen SZ, Adams PH, Isherwood I. Measurement of trabecular bone mineral by dual energy computed tomography. *J Comput Assist Tomogr* 1982; 6:601-607.

55. Laval-Jeannette AM, Roger B, Bouysse S, Bergot C, Mazess RB. Influence of vertebral fat content upon quantitative CT density. *Radiology* 1986; **159**:463-466.
56. Hall FM, Davis MA, Baran DT. Bone mineral screening for osteoporosis. *N Engl J Med* 1987; **316**:212-214.
57. Health and Public Policy Committee, American College of Physicians. Radiologic methods to evaluate bone mineral content. *Ann Intern Med* 1984; **100**:908-911.
58. Health and Public Policy Committee, American College of Physicians. Bone Mineral Densitometry. *Ann Intern Med* 1987; **107**:932-936.
59. Ott SM, Kilcoyne RF, Chestnut CH III. Ability of four different techniques of measuring bone mass to diagnose vertebral fractures in postmenopausal women. *J Bone Mineral Res* 1987; **3**:201-210.
60. Cummings SR, Black D. Should perimenopausal women be screened for osteoporosis? *Ann Intern Med* 1986; **104**:817-823.
61. Horsman A, Jones M, Francis R, Nordin C. The effect of estrogen dose on postmenopausal bone loss. *N Engl J Med* 1983; **309**:1405-1407.
62. Ettinger B, Genant HK, Cann CE. Long-term estrogen replacement therapy prevents bone loss and fractures. *Ann Intern Med* 1985; **102**:319-324.
63. Paganini-Hill A, Ross RK, Gerkins VR, Henderson BE, Arthur M, Mack TM. Menopausal estrogen therapy and hip fractures. *Ann Intern Med* 1981; **95**:28-31.
64. Ross RK, Paganini-Hill A, Gerkins VR, et al. A case-control study of menopausal estrogen therapy and breast cancer. *JAMA* 1980; **243**:1635-1639.
65. Mack TM, Pike MC, Henderson BE, et al. Estrogens and endometrial cancer in a retirement community. *N Engl J Med* 1976; **294**:1262-1267.
66. Shaprio S, Kelly JP, Rosenberg L, Kaufman DW, et al. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. *N Engl J Med* 1985; **313**:969-972.
67. Kaufman DW, Miller DR, Rosenberg L, Helmrich SP, et al. Noncontraceptive estrogen use and the risk of breast cancer. *JAMA* 1984; **252**:63-67.
68. Weiss NS, Szkely DR, English DR, Schweid AI. Endometrial cancer in relation to patterns of menopausal estrogen use. *JAMA* 1979; **242**:261-264.
69. Hillner BE, Hollenberg JP, Pauker SG. Postmenopausal estrogens in prevention of osteoporosis. Benefit virtually without risk if cardiovascular effects are considered. *Am J Med* 1986; **80**:1115-1127.
70. Gambrell RD, Massey FM, Castaneda TA, Ugenas AJ, Ricci, CA. Reduced incidence of endometrial cancer among postmenopausal women treated with progestogens. *J Am Geriatr Soc* 1979; **27**:389-394.
71. Whitehead MI, Townsend PT, Pryse-Davies J, Ryder TA, King RJB. Effects of estrogens and progestins in the biochemistry and morphology of the postmenopausal endometrium. *N Engl J Med* 1981; **305**:1599-1605.
72. Lane G, Siddle NC, Ryder TA, Pryse-Davies J, King RJB, Whitehead MJ. Is provera the ideal progestogen for addition to postmenopausal estrogen therapy? *Fertil Steril* 1986; **45**:345-352.
73. Riggs BL, Seeman E, Hodgson SF, Taves DR, O'Fallon WM. Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. Comparison with conventional therapy. *N Engl J Med* 1982; **306**:446-450.
74. Kanis JA, Meunier PJ. Should we use fluoride to treat osteoporosis? A review. *Q J Med* 1984; **53**:145-164.
75. Eriksen EF, Mosekilde L, Melsen F. Effect of sodium fluoride, calcium, phosphate, and vitamin D₂ on trabecular bone balance and remodeling in osteoporotics. *Bone* 1985; **6**:381-389.
76. O'Duffy JD, Wahner HW, O'Fallon WM, et al. Mechanism of acute lower extremity pain syndrome in fluoride-treated osteoporotic patients. *Am J Med* 1986; **80**:561-566.
77. Pak CYC, Sakhae EK, Gallagher C, et al. Attainment of therapeutic fluoride levels in serum without major side effects using a slow-release preparation of sodium fluoride in postmenopausal osteoporosis. *J Bone Mineral Res* 1986; **1**:563-571.
78. Gruber HE, Ivey JL, Baylink DJ, et al. Long-term calcitonin therapy in postmenopausal osteoporosis. *Metabolism* 1984; **33**:295-303.
79. Aloia JE. Calcitonin and osteoporosis. *Geriatric Medicine Today* 1985; **4**(11):20-28.
80. Mazzuoli GF, Passeri M, Gennari C, et al. Effects of salmon calcitonin in postmenopausal osteoporosis: a controlled double-blind clinical study. *Calcif Tissue Int* 1986; **38**:3-8.
81. Zorzini L, Capone M. Postmenopausal osteoporosis: therapeutic and side effects of different calcitonins. *Curr Therapeutic Res* 1984; **36**:473-482.
82. Chestnut CH, Ivey JL, Gruber HE. Stanazolol in postmenopausal osteoporosis: therapeutic efficacy and possible mechanisms of action. *Metabolism* 1983; **32**:571-575.
83. Aloia JE, Kapoor A, Vaswani A, Cohn SH. Changes in body composition following therapy of osteoporosis with methandrostenolone. *Metabolism* 1981; **30**:1076-1079.
84. Bijlsma JWJ, Duursma SA, Bosch R, Huber O. Lack of influence of the anabolic steroid nandrolonedecanoate on bone metabolism. *Acta Endocrinologica* 1982; **101**:140-143.
85. Frost HM. Treatment of osteoporosis by manipulation of coherent bone cell populations. *Clin Orthop* 1979; **143**:227-244.
86. Anderson C, Cape RDT, Crilly RG, Hodsman AB, Wolfe BMJ. Preliminary observations of a form of coherence therapy for osteoporosis. *Calcif Tissue Int* 1984; **36**:341-343.
87. Rasmussen H, Bordier RF, Marie P, et al. Effect of combined therapy with phosphate and calcitonin on bone volume in osteoporosis. *Metab Bone Dis Relat Res* 1980; **2**:107-111.
88. Slovik DM, Rosenthal DI, Doppelt SH, et al. Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1-34) and 1,25-dihydroxyvitamin D. *J Bone Mineral Res* 1986; **1**:377-381.