tric testing. As reflected in table 1, 86.4 percent of the women who were screened and found to have a low bone mass altered their lifestyle, compared with 68.7 percent of normopenic screenees and 53.8 percent of the unscreened population. The most obvious changes in all groups were in exercise and diet.

Conclusions

The postmenopausal population of the United States is increasing at a rapid rate, and life expectancy for a woman is now 78 or more years. Since all women will experience menopause, much can be done to ensure that their postmenopausal years will be quality years. A significant minority of these women will be subject to chronic diseases that may be averted by the selective and judicious use of hormone additive therapy. Clinicians and other health care professionals need to be trained in techniques that will help identify women at risk, thereby individualizing the need for hormone therapy. Combined with exercise and other life-style measures, the process of middle-age aging can be altered to ensure greater productivity and health, with an equally important reward of better health, and thus enjoyment, in older age

References

1. Statistical Abstract of the United States, 1984. U.S. Department of Commerce, Bureau of the Census. 104th ed., p. 409.
2. Tulandi, T., and Lal, S.: Menopausal hot flush. Obstet Gynecol Surv 40: 553-563 (1985).
3. Schiff, I., et al.: Oral medroxyprogesterone in the treatment of postmenopausal symptoms. JAMA 244: 1443-1450, Sept. 26, 1980.
4. Schiff, I., et al.: Effects of estrogens on sleep and psychological state of hypogonadal women. JAMA 242: 2405-2407, Nov. 30, 1979.
5. Ballinger, C.B.: Psychiatric morbidity and the menopause. Screening of the general population sample. Br Med J 3 (5979): 344-346, Aug. 9, 1975.
6. Ballinger, C.B.: Psychiatric morbidity and the menopause. Survey of gynaecological outpatient clinic. Br J Psych 131: 83-89 (1977).
7. Montgomery, J.C., et al.: Effect of oestrogen and testosterone implants on psychological disorders in the climacteric. Lancet 8554 (i): 297-299, Aug. 8, 1987.
8. Campbell, S., and Whitehead, M.: Oestrogen therapy and the menopausal syndrome. Clin Obstet Gynecol 4: 31-48 (1977).
9. Kannel, W.B., and Gordon, T.: Cardiovascular effects of the menopause. *In* Menopause: physiology and pharmacology, edited by D. Mishell. Year Book Publishers, Chicago and London, 1987, pp. 91-102.
10. Ross, R.K., et al.: Estrogen use and cardiovascular disease. *In* Menopause: physiology and pharmacology, edited by D. Mishell. Year Book Publishers, Chicago and London, 1987, pp. 209-224.
11. Lindsay, R., et al.: Long-term prevention of postmenopausal osteoporosis by oestrogen. Evidence for an increased bone mass after delayed onset of oestrogen treatment. Lancet 7968 (i) 1038-1041, May 15, 1976.
12. Ettinger, B., Genant, H., and Cann, C.E.: Long-term estrogen replacement therapy prevents bone loss and fractures. Ann Intern Med 102: 319-324 (1985)
13. Notelovitz, M.: The role of the gynecologist in osteoporosis prevention: a clinical approach. Clin Obstet Gynecol 30: 871-882 (1987).
14. Lindsay, R., Hart, D.M., Forrest, C., and Baird, C.: Prevention of spinal osteoporosis in oophorectomized women. Lancet 8205 (ii): 1151-1154, Nov. 29, 1980.
15. Weiss, N.S., et al.: Decreased risk of fractures of the forearm with postmenopausal use of estrogen. N Engl J Med 303: 1195-1198, Nov. 20, 1980.
16. Weinstein, L.: Efficacy of a continuous estrogen-progestin regimen in the menopausal patient. Obstet Gynecol 69: 929-932 (1987).
17. Padwick, M., et al.: A simple method for determining the optimal dosage of progestin in postmenopausal women receiving estrogens. N Engl J Med 315: 930-934 (1986).
18. Notelovitz, M.: Post-menopausal osteoporosis: a practical approach to its prevention. Acta Obstet Gynecol Scand Suppl 134: 67-80 (1986).

Panel Session: Prevention/Treatment

Treatment of Osteoporotic Patients

C. CONRAD JOHNSTON, JR., MD

Dr. Johnston is Professor of Medicine, Indiana University Medical Center, Indianapolis, IN. This article is based on his presentation at the FDA Special Topic Conference on Osteoporosis, sponsored by the Food and Drug Administration, held at Bethesda, MD, October 30, 1987.

Synopsis

The best approach to treatment of osteoporosis is prevention of bone loss as discussed elsewhere in this volume. However, some currently approved therapeutic agents are helpful in the management of the patient who presents with an osteoporotic fracture. These agents include an adequate calcium intake, estrogen replacement therapy, and administration of calcitonin.

A number of experimental therapies are being evaluated, providing hope for improved treatment in the future. These include sodium fluoride, low-dose parathyroid hormone, anabolic steroids, various forms of cyclical therapy, growth hormone, and various bone growth factors.

THE GOAL IN THE TREATMENT of the patient with osteoporosis who has a fracture is to prevent the development of further fractures. Ideally, this should be accomplished by increasing bone mass at the site of fracture, usually the vertebra or hip, to the point that fracture incidence is reduced. However, none of the currently approved therapeutic agents can increase bone mass to a very great extent. Nevertheless, fracture incidence may be reduced with their use.

Fracture pathogenesis is complex. Low bone mass at the site of fracture is a necessary, but not sufficient cause to explain all of the fractures that occur in elderly individuals, all of whom have lost bone. Other factors may be important. Those that are intrinsic to the skeleton are low bone mass, architectural abnormalities, osteomalacia, and slow remodeling. Those that are extrinsic to the skeleton are increased frequency of trauma (falling) and diminished energy absorption by soft tissue.

Architectural abnormalities are produced by loss of trabeculae (*1*), which cannot be replaced with currently available therapies. This observation emphasizes the necessity for prevention of bone loss in individuals at risk. Osteomalacia occurs in some patients with osteoporosis, especially elderly individuals with hip fracture (*2*). Unfortunately, this potentially treatable contributing factor is difficult to diagnose using currently available means (*3*), with the exception of bone biopsy. The adult skeleton is constantly renewed by the process of remodeling (*4*), and when this process slows, microdamage may accumulate and lead to spontaneous fractures. Bone loss slows in the elderly (*5*), yet hip fracture incidence continues to rise. This continued increase probably is the result of the increased frequency of trauma from falling (*6*). Investigation of causes of falling may lead to other areas of intervention to reduce fractures.

Currently Approved Therapy

Currently approved agents that can be utilized to treat the patient with a fracture (especially vertebral crush fractures) include calcium, estrogen replacement therapy (ERT), and calcitonin. Calcium, and especially estrogen, are important agents used in the prevention of bone loss, but some evidence suggests that they also reduce the incidence of vertebral height and presumably of fractures in patients who already have fractures (*7*). The mechanism for this protection is not clear, since neither agent produces a marked increase in bone mass. An adequate calcium intake can be prescribed for all of the population.

ERT (estrogen alone or estrogen and a progestin) is most effective in preserving bone mass if it is used when the patient is close to menopause, but is still effective in women up to 65 or 70 years of age. (*8*).

Calcitonin is approved for treatment of patients with osteoporotic fractures. Calcitonin significantly increases total body calcium as measured by neutron activation (*9*), and bone mass in the spine and distal radius (*10, 11*). However, the drug may lose its positive effect with time, and, in addition, the medication must be given by injection, and is rather expensive.

Calcium, ERT, and calcitonin provide help for the patient with osteoporotic fractures, although none of these agents is ideal because they do not restore bone mass to normal. Investigational agents provide hope for better forms of intervention in the future.

Investigational Agents

A number of regimens are currently being studied for use in the osteoporotic patient. These include fluoride, low-dose parathyroid hormone (PTH), anabolic steroids, cyclical therapy (etidronate, phosphate-calcitonin, phosphate-etidronate), growth hormone, and growth factor.

Fluoride has probably received the most extensive study (*12*). It can dramatically increase vertebral bone mass in patients who respond (*13*), yet many questions remain unanswered. All persons do not respond to the drug, and in those who do respond, the effect is principally on trabecular bone. A positive effect on cortical bone may be necessary to reduce the incidence of hip fractures. In addition, fluoride produces side effects, including gastrointestinal distress, and periarticular pain. The new bone formed under the influence of fluoride is not entirely normal and, as yet, no data on decreased rates of fracture have been published from properly controlled trials.

A number of other investigational agents are under study. Low-dose PTH has been shown to increase

trabecular bone mass in a limited number of patients (*14*). Anabolic steroids have also been shown to increase bone mass, as measured by neutron activation (*15*). However, most currently available drugs of this type appear to have adverse clinical effects on serum lipids, and thus have very limited clinical usefulness. Several forms of cyclical therapy have also been proposed. These include use of etidronate, or phosphate and calcitonin. A method called ADFR (Activate, Depress, Free, Repeat) has also been proposed for treatment of osteoporosis (*16*). In ADFR, the remodeling cycles are coherently activated by an agent, and osteoclast activity is depressed with another agent. Osteoblasts are allowed to produce their normal quantum of bone during a free period, and the process is then repeated. Activators such as phosphate and PTH, and depressors such as calcium, calcitonin, or phosphonates may prove successful in this scheme. Finally, growth hormone, or one of the many proposed bone growth factors, may be of value.

All of these investigational regimens show promise of effectiveness, but *all* require further study. As noted, the ultimate goal is a reduction in fracture incidence. This may be difficult to demonstrate because of the large numbers of patients required if clinical fractures are used as an endpoint (*17*). A reduction in vertebral deformity may serve as a suitable surrogate. In addition, a positive effect may be suggested if there is a significant increase in bone mass at the site of the fracture, and the bone is of normal quality. Since remodeling is slow in older persons, the effect on bone mass must be shown to persist, and not simply be a transient phenomenon. This probably requires follow-up for at least 3 years.

Conclusions

The best approach to the treatment of osteoporosis is prevention of bone loss. This is particularly true because some of the architectural changes which occur in trabecular bone are reversible. However, currently approved therapeutic agents can provide help for the patient who has an osteoporotic fracture. These agents include calcium, ERT, and calcitonin. A number of new therapeutic regimens are under investigation, which may lead to more effective interventions in the future. The ideal agent would increase bone mass at the site where fractures occur to a degree that fracture incidence is reduced.

References

1. Parfitt, A.M., et al.: 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 72: 1396–1409 (1983).
2. Johnston, C.C., Peacock, M., and Meunier, P.: Osteomalacia as a risk factor for hip fractures in the U.S.A. *In* Osteoporosis 1987, edited by C. Christiansen, J.S. Johansen, and B.J. Riis. Norhaven Bogtrykken A.S., Viborg. In press, 1988.
3. Hordon, L.D., and Peacock, M.: Vitamin D. metabolism in women with femoral neck fracture. Bone Miner 2: 413–426, August 1987.
4. Frost, H.M.: The skeletal intermediary organization: a synthesis. *In* Bone and mineral research, edited by W.A. Peck. Elsevier Science Publishers B.V., Amsterdam, 1985, 3: 49–107.
5. 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).
6. Melton, L.J., III, and Riggs, B.L.: Risk factors for injury after a fall. Clin Geriatr Med 1: 525–539, August 1985.
7. Riggs, B.L., et al.: Effect of the fluoride/calcium regimen on vertebral fracture occurrence in postmenopausal osteoporosis. N Eng J Med 306: 446–450, Feb. 25, 1982.
8. 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, June 1987.
9. Gruber, H.E., et al.: Long-term calcitonin therapy in postmenopausal osteoporosis. Metabolism 33: 295–303 (1984).
10. Gennari, C., et al.: Comparative effects on bone mineral content of calcium and calcium plus salmon calcitonin given in two different regimens in postmenopausal osteoporosis. Curr Ther Res 38: 455–464 (1985).
11. Mazzuoli, G.F., et al.: Effects of salmon calcitonin in postmenopausal osteoporosis: a controlled double-blind clinical study. Calcif Tissue Int 38: 3–8 (1986).
12. Riggs, B.L.: Treatment of osteoporosis with sodium fluoride: an appraisal. *In* Bone and mineral research, edited by W.A. Peck. Elsevier Publishers B.V., Amsterdam, 1984, 2: 366–393.
13. Kanis, J.A., and Meunier, P.J.: Should we use fluoride to treat osteoporosis?: a review. Q J Med 210: 145–164, Spring 1984.
14. Slovik, D.M., et al.: Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1-34) and 1, 25-dihydroxyvitamin D. J Bone Miner Res 1: 377–381 (1986).
15. Chesnut, C.H., et al.: Stanozolol in postmenopausal osteoporosis: therapeutic efficacy and possible mechanisms of action. Metabolism 32: 571–580 (1983).
16. Frost, H.M.: Treatment of osteoporosis by manipulation of coherent bone cell populations. Clin Orthop Relat Res 143: 228–244 (1979).
17. Rich, C., et al.: Factors involved in an objective study of the efficacy of treatment of osteoporosis. Clin Orthop 45: 63–66 (1966).