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C. Conrad Johnston

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C. Conrad Johnston, Jr, MD*

Ed. Note - This overview was originally presented at the International Symposium on Clinical Disorders of Bone and Mineral Metabolism, May 9-13, 1983. The following list indicates the presentations given in this session at the Symposium and the contents of the corresponding chapter in the Proceedings of the Symposium published by Excerpta Medica. The numbers in parentheses refer to pages in this volume. Complete information about the contents of the Proceedings can be found at the back of this issue.

The determinants of bone volume in young adults. J. Aaron, K. Sagreiya, D. Carter, and B.E.C. Nordin (323)

Microstructural and cellular basis of age-related bone loss and osteoporosis. A.M. Parfitt, C.H.E. Mathews, A.R. Vilanueva, D.S. Rao, M. Rogers, M. Kleerekoper, and B. Frame (328)

Determinants of age-related bone loss. R.P. Heaney (333)

Heterogeneity of involutional osteoporosis: Evidence for two distinct osteoporosis syndromes. B.L. Riggs, L.J. Melton III, and H.W. Wahner (337)

Steroid-induced osteoporosis. L.V. Avioli (343)

Can estrogen therapy prevent bone loss? R. Lindsay (346)

A model for establishing optimal prophylaxis and treatment in postmenopausal osteoporosis. C. Christiansen, P. Rodbro, and L. Tjellesen (349)

Anabolic steroids and calcitonin in the treatment of postmenopausal osteoporosis. C.H. Chesnut III, D.J. Baylink, H.E. Gruber, J. Ivey, M. Matthews, W.B. Nelp, and K. Sisom (355)

Treatment of idiopathic osteoporosis with sodium fluoride. P.J. Meunier, K. Galus, D. Briancon, C. Edouard, and S.A. Charhon (360)

The use of calcitrol (1,25 dihydroxyvitamin D) in osteoporosis. J.C. Gallagher (364)

Osteopenia: The ADFR treatment. H.M. Frost (368)

Pathogenesis

Osteoporosis is the most common of the metabolic bone diseases. A number of papers presented at this symposium have indicated the progress made in this field, relating both to the pathogenesis of the disease and to its prevention and treatment.

Nordin, et al (pp. 323 ff.) reported additional data to support their model for the determination of bone volume by an independent variable (bone formation rate) and a volume-dependent variable (fractional bone resorption). In this case, mean-seam width was used as an index of formation in biopsies from a group of premenopausal women in a state of equilibrium, when formation and resorption are balanced. Again, previously reported correlations were found. Nordin feels that age-related bone loss is associated with an increase in resorption, which is more marked in those who develop osteoporosis. The principal disagreement here is with the methods used to estimate rates of resorption and bone formation—measurement of resorption and formation surfaces. Many investigators feel that rates cannot be derived from static surface measurements. Nordin emphasizes the importance of the model or formation as an independent variable, and believes that substitution of other measures (i.e., the calcification rate derived from tetracycline labeling) would only shift the curve and would not alter the fundamental concept. Clearly, additional data using multiple methods to correlate change over time will be needed to resolve this dilemma.

Parfitt, et al (p. 328 ff.) addressed the important problem of age-related loss of trabecular bone from a new perspective. Is this loss of trabecular bone due to a decrease in the number (density) of trabeculae or to a decrease in the thickness of individual trabeculae? His studies indi-

*Indiana University School of Medicine, Indianapolis
Address reprint requests to Dr. Johnston, Indiana University School of Medicine, 545 Barnhill Drive, Emerson Hall 421, Indianapolis, IN 46223.

cate that both mechanisms are in part responsible, but loss of trabeculae is the predominant mechanism, both for age-related loss and for the more marked deficit found among osteoporotics. A reduction in the mean-wall thickness of individual structural units can explain the thinness of individual trabeculae but not total loss of the structure. He suggests that during the accelerated phase of bone loss, shortly after menopause, osteoclasts perforate trabeculae; thus, there is no remaining structure upon which new bone can be rebuilt. A similar mechanism may be responsible for endosteal bone loss.

Studies utilizing tetracycline labeling as a measure of bone apposition indicate that osteoblast function declines with age in normal individuals and, to a more marked degree, in osteoporotics. After menopause, the increase in bone remodeling persists for some time. Among some who will develop osteoporosis, the rapid remodeling ceases for unknown reasons, and this cessation may be an important factor in fracture pathogenesis. He suggests that some osteoporotics start with low bone mass at maturity and have a prolonged phase of accelerated bone loss, the result of which is low bone mass and fracture. These individuals would have high remodeling on biopsies taken at the time of fracture. Others have rapid loss but are unable to compensate, and decreased remodeling is found on biopsy. Thus, the heterogeneity of morphometric variables in osteoporosis can be explained.

Parfitt presented a new hypothesis which places great emphasis on loss of structural elements due to increased osteoclast activity. Because this phenomenon occurs years before fracture, prevention and treatment must focus on the years associated with rapid bone loss, shortly after the menopause. Nordin stressed increased resorption as the primary event responsible for bone loss in osteoporosis. Measured variables are derived from static measurement of bone surfaces at the time of fracture. Parfitt emphasized that most of the bone loss is due to removal of structural elements during the rapid phase of bone loss after the menopause, and this loss is due to osteoclast penetration of existing trabeculae. Could the increased resorption surfaces seen by Nordin reflect the previous activity postulated by Parfitt? Clearly, additional studies are necessary, but the focus of research should shift from the patient with the disease (fracture) to the individual who loses bone at a rapid rate some years before the morbid event.

Low bone mass is one of the principal determinants of osteoporotic fractures. Heaney, et al (pp. 333 ff.) reviewed the complex mechanisms responsible for determination of bone mass in the aging individual. Four elements are important: 1) peak bone mass achieved; 2) remodeling balance; 3) remodeling rate; and 4) time. Many factors may affect the first three variables to produce the bone mass found at any time.

Mechanical loading, perhaps through direct or indirect stimulation of osteoblasts (thereby producing a positive remodeling balance) may be important, both in attainment of peak adult bone mass and in subsequent rates of loss. With age, there is a reduction of peak strains induced, rate of strain, and diversity of activity performed. These factors may lead to a negative remodeling balance and bone loss.

Remodeling rates may be determined primarily by parathyroid hormone secretion. In the presence of a negative remodeling balance, such as is found in aging individuals, an increase in remodeling rate would lead to more rapid loss of bone. Increased effective calcium intake will suppress parathyroid hormone (PTH) and, thus, remodeling. It is not entirely clear whether calcium intake within the usually-expected range affects bone loss, but inadequate intake certainly could accelerate loss caused by other factors. Other nutrients may negatively affect calcium balance as well, especially excessive intakes of protein and alcohol.

Estrogen deficiency is associated with accelerated bone loss, although the mechanisms are not clear. Remodeling rates are increased by estrogen withdrawal, and in the presence of a negative remodeling balance, more rapid loss would ensue. Estrogen also appears to affect calcium homeostatic mechanisms, which lead to more effective absorption from gut, renal calcium conservation, and a blunted PTH effect.

Calcitonin may play a role in age-related bone loss, but this role remains to be clearly delineated; also, accumulation of structural errors, such as perforation of trabeculae by excessive osteoclastic resorption (as suggested by Parfitt), may be important.

Clearly, many factors are important in the determination of bone mass, and it is only through a better understanding of these mechanisms that a rational approach to prevention of bone loss can be derived.

It has generally been assumed that osteoporotic fractures of the vertebrae, distal radius, and hip have a similar pathogenesis. However, Riggs, et al (pp. 337 ff.) suggested that there are several osteoporotic syndromes. Type 1 osteoporosis is associated with excessive trabecular bone loss and leads to vertebral collapse fractures and to Colles fractures, especially among women 50 to 65 years of age. It is postulated that estrogen deficiency leads to an increased bone sensitivity to the action of PTH, and that

this activity causes loss of bone. The calcium mobilized with bone loss reduces PTH secretion but not enough to prevent excessive bone loss. However, since serum PTH concentration is reduced, less $1,25(OH)_2D_3$ is synthesized by the kidney, and calcium malabsorption ensues. Since all women are estrogen-deficient after menopause, and no measured difference in sex hormone concentrations has been found between the majority who do not develop osteoporosis and the small group who do, Riggs postulated that there is some undefined intrinsic abnormality of bone which predisposes to excessive loss with estrogen deficiency. Nordin has suggested that the osteoporotics have more marked calcium malabsorption, which should lead to increased secretion of PTH, and Riggs has found PTH concentrations to be low in this group, compared to controls. Thus, the predisposing factors remain to be determined.

Type 2 osteoporosis is associated with the loss of both trabecular and cortical bone, and eventually leads to hip and vertebral fractures. It occurs primarily in individuals over 75; although more common in women, it also affects men. It is postulated that a primary defect in $1,25(OH)_2D_3$ synthesis leads to calcium malabsorption and secondary hyperparathyroidism with increased bone turnover. Since there is a negative remodeling balance at individual sites, bone loss occurs.

Riggs, his associates, and others have accumulated evidence that the different fracture syndromes generally associated with osteoporosis may be due to different mechanisms of bone loss. This concept is important in designing effective programs for prophylaxis and treatment. Clearly, we would not wish to introduce a therapeutic program to prevent one fracture type that would lead to a greater risk of developing another fracture syndrome.

The important clinical problem of steroid-induced osteoporosis was reviewed by Avioli (pp. 343 ff.). Glucocorticoids seem to produce loss of trabecular bone primarily and, thus, vertebral fractures. The effect is dose and time dependent, but it can occur with as little as 7 mg of prednisone a day or its equivalent. Those particularly at risk are growing children, postmenopausal women, and those receiving other drugs which may affect the skeleton, such as anti-convulsants. Glucocorticoids have multiple effects that are responsible for bone loss, including impaired calcium absorption, increased calcium excretion by the kidney, and impaired osteoblast function.

No effective means is currently available to prevent these complications, other than reduction in dose and time of administration when possible. A new glucocorticoid under development, Deflazacort, shows promise of being less deleterious to mineral homeostatis than currently available drugs.

Prevention and Treatment

The treatment of osteoporosis must be considered from the standpoint of both prevention of bone loss and therapy of the patient after fracture has occurred. Lindsay (pp. 346 ff.) reviewed the evidence that administration of estrogen can prevent loss of bone in postmenopausal women. This effect has been demonstrated, using techniques which measure both cortical and trabecular bone. With therapy, bone loss can be prevented up to eight years, when slow loss may begin. When estrogen is withdrawn, loss ensues, but it is no greater than the loss occurring after natural menopause. Administration of estrogen is also associated with less loss of height and fewer vertebral deformities than occur in placebo-treated controls. Christiansen, et al (pp. 349 ff.) also noted that a combination of estrogen and progesterone prevents cortical bone loss. The principal problem of prophylaxis with estrogen is the determination of who should receive the drug, since it can be toxic. Christiansen has found that there is a population of rapid bone losers that, he predicts, will develop osteoporosis. There women have lower estrogen concentrations, higher serum alkaline phosphatase, and higher urinary hydroxyproline/creatinine ratios than those who lose bone more slowly. While this problem requires additional study, these data provide promising leads to the development of a simple screening procedure to select women for prophylactic estrogen therapy shortly after the onset of menopause.

Chesnut and associates (pp. 355 ff.) demonstrated that administration of calcitonin to patients with osteoporotic fractures led to an increase in total body calcium, as measured by neutron activation. This increase persisted for 18 months, but by 26 months the rate of gain was not sustained; no change in regional bone mass could be measured by photon absorptiometry. The patients tolerated the calcitonin well with few adverse reactions. This group has also demonstrated that administration of stanozolol to a similar population of postmenopausal osteoporotic patients was associated with a significant increase in total body calcium at 26 months on therapy. The magnitude of the increase in calcium retention seemed to persist throughout the study. Analysis of biochemical and histologic data suggested that the effect of the drug was to stimulate bone formation. Transient elevations in SGOT were noted in some patients, as well as some evidence of increased facial hair, ankle edema, and hoarseness. Neither study contained sufficient numbers of patients to determine whether the incidence of fractures was reduced.

Meunier, et al (pp. 360 ff.) presented data on 57 osteoporotic patients treated for two years with a combination of sodium fluoride, calcium, and vitamin D. No control group was included. Fifty-six percent of the patients experienced relief from back pain after two years of therapy. The incidence of vertebral fracture was lower in the second year of treatment than in the first, and the mean annual increase in the radiological vertebral index was also lower during the second year. No significant changes were found in the biochemical parameters measured. Bone biopsies were performed before and after treatment in 11 patients classified as good responders; there was a marked increase in the osteoid surfaces and osteoblastic surfaces without an increase in the resorption surfaces. The increase in trabecular bone volume was also marked in these biopsies. The newly-formed bone was lamellar in character. No microradiographs were performed, but some evidence in the literature suggests that newly-formed bone is not as well calcified as normal bone. Side effects consisted of mild gastrointestinal irritation in 22% of the patients and transient periarticular pain in 33%, but only 7% of the patients discontinued therapy because of adverse reactions. Some patients treated with fluoride did not appear to respond to the therapy. Meunier found that some showed no response on formation surfaces, while others had increased formation surfaces but did not gain bone. The mechanisms for these changes remain to be elucidated.

Initial studies have been undertaken to evaluate the effect of $1,25(OH)_2D_3$. When this drug was given in a preliminary study, bone volume increased significantly at 24 months, as measured on iliac crest biopsies. The calcium balance improved so that it was positive after six months, but subsequently a less positive balance was found. There appeared to be a significant decrease in vertebral fractures in the treated group. Additional studies will be necessary to evaluate this therapeutic agent in the treatment of osteoporosis.

A new approach to the treatment of osteoporosis, the "ADFR" method, has been developed. Currently under evaluation, this method was reviewed by Frost (pp. 368 ff.). An agent known to activate bone remodeling is adminstered in pulsatile fashion in order to activate a number of the bone remodeling units simultaneously. A medication which will depress osteoclastic activity during the resorptive phase is then administered, thus reducing the amount of bone removed. Subsequently, a free period is allowed so that the osteoblasts will replace their programmed quantum of bone. Since the osteoclasts have removed less bone, bone balance will be positive. The entire sequence can then be repeated. This method was developed based on the current understanding of bone function as an organ. Preliminary data from animal studies appear to indicate that the sequence will produce its desired effect.

Progress has been made over the past decade in our understanding of osteoporosis. Use of the bone biopsy has led to a better understanding of the pathogenesis of age-related bone loss, although controversy still remains. Efforts should be focused on that period of rapid bone loss that occurs shortly after menopause. Many factors may be important in the development of maximum adult bone mass and its subsequent rate of loss, including mechanical loading, hormonal influences, and nutrition factors. These all provide fertile areas for additional research during the next few years. Since the fracture syndromes generally associated with osteoporosis may be due to different pathogenic mechanisms, an approach to prevention and treatment may require awareness of this heterogeneity. The application of the ADFR theory may allow even further advances. As progress is made to identify patients who will subsequently be at risk of fracture, a rational prophylaxis can be designed. The next decade should provide exciting new insights into the pathogenesis and treatment of osteoporosis.