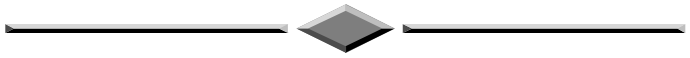
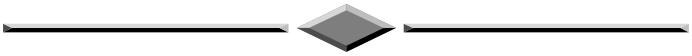
NIH Consensus Development Conference on Osteoporosis Prevention, Diagnosis, and Therapy



March 27–29, 2000
William H. Natcher Conference Center
National Institutes of Health
Bethesda, Maryland



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Introduction

Osteoporosis is a major threat for millions of Americans. In the United States today, 10 million individuals already have osteoporosis, and 18 million more have low bone mass, placing them at increased risk for this disease. Osteoporosis is characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures, especially of the hip, spine, and wrist. It is the most prevalent of the bone diseases that affect Americans, and women are four times more likely to develop osteoporosis than men.

Osteoporosis, once acknowledged as a natural part of aging, does not need to be a consequence of aging any longer. It is largely a preventable disease due to the remarkable progress that has been made in the scientific understanding of its causes, diagnosis, and treatment.

To clarify the factors associated with prevention and better diagnosis and treatment of osteoporosis among health care providers and the public, the NIH has organized this 2½-day conference to present the latest information on the disease. After 1½ days of presentations and audience discussion addressing the latest in osteoporosis research, an independent, non-Federal consensus development panel will weigh the scientific evidence and write a draft statement that will then be presented to the audience on the third day. The consensus development panel's statement will address the following key questions:

- What is osteoporosis and what are its consequences?
- How do risks vary among different segments of the population?
- What factors are involved in building and maintaining skeletal health throughout life?
- What is the optimal evaluation and treatment of osteoporosis and fractures?
- What are the directions for future research?

General Information

Conference sessions will be held in the Natcher Conference Center (Building 45), NIH, 9000 Rockville Pike, Bethesda, Maryland. Registration begins at 7:30 a.m. on Monday and Tuesday and 8 a.m. on Wednesday, and conference sessions will run from 8 a.m. to 6 p.m. on Monday, 8:30 a.m. to 12:30 p.m. on Tuesday, and 9 a.m. to 11 a.m. on Wednesday. The telephone number for the message center is (301) 496-9966; the fax number is (301) 480-5982.

Cafeteria

The cafeteria in the Natcher Conference Center is located one floor above the auditorium on the main floor of the building. It is open from 7 a.m. to 2 p.m., serving breakfast and lunch.

Sponsors

The primary sponsors of this meeting are the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the NIH Office of Medical Applications of Research. The conference is cosponsored by the National Institute on Aging; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Dental and Craniofacial Research; National Institute of Child Health and Human Development; National Institute of Nursing Research; National Institute of Environmental Health Sciences; National Heart, Lung, and Blood Institute; NIH Office of Research on Women's Health; and Agency for Healthcare Research and Quality (formerly the Agency for Health Care Policy and Research).

Conflict of Interest

In accordance with ACCME requirements regarding conflict of interest, each speaker presenting at this conference has been asked to submit documentation outlining any real or potential conflict of interest.

Agenda

Monday, March 27, 2000

7:30 a.m. Registration

8:00 a.m. Opening Remarks
Stephen I. Katz, M.D., Ph.D., Director
National Institute of Arthritis and Musculoskeletal and Skin Diseases

8:10 a.m. Charge to the Panel
Stephen C. Groft, Pharm.D., Acting Director
NIH Office of Medical Applications of Research

8:20 a.m. Panel and Conference Chair Remarks
Anne Klibanski, M.D., Professor of Medicine, Harvard Medical School
Chief, Neuroendocrine Unit, Massachusetts General Hospital

I. Overview

8:30 a.m. The Pathophysiology of Osteoporosis
B. Lawrence Riggs, M.D., Staff Consultant
Division of Endocrinology, Mayo Clinic and Mayo Foundation

8:45 a.m. Biomechanics of Osteoporotic Fractures
Mary L. Bouxsein, Ph.D., Instructor
Department of Orthopaedic Surgery, Orthopaedic Biomechanics Laboratory
Beth Israel Deaconess Medical Center

II. Epidemiology

9:00 a.m. Osteoporosis in 2000
L. Joseph Melton III, M.D., Michael M. Eisenberg Professor
Department of Health Sciences Research, Mayo Clinic and Mayo Foundation

9:15 a.m. Clinical Implications of Bone Density Variation Among Different Populations
Richard D. Wasnich, M.D., F.A.C.P., Director
Hawaii Osteoporosis Center

9:30 a.m. Osteoporosis in Men
Eric S. Orwoll, M.D., Professor of Medicine
Oregon Health Sciences University

9:45 a.m. Discussion

Monday, March 27, 2000 (continued)

III. Osteoporosis Risks and Prevention Opportunities

10:15 a.m. Genetics of Age-Related Osteoporosis
Munro Peacock, M.D., Professor of Medicine
General Clinical Research Center, Indiana University Medical Center

10:30 a.m. Nutrition—Beyond Calcium
Robert P. Heaney, M.D., John A. Creighton University Professor
Professor of Medicine, Department of Medicine, Creighton University

10:45 a.m. The Role of Calcium in the Prevention and Treatment of Osteoporosis
Bess Dawson-Hughes, M.D., Professor of Medicine
Chief, Calcium and Bone Metabolism Laboratory
Jean Mayer USDA Human Nutrition Research Center on Aging
Tufts University

11:00 a.m. The Skeletal Effects of Exercise
Robert A. Marcus, M.D., Professor of Medicine
Stanford University, VA Medical Center

11:15 a.m. Peak Bone Mass—Peak Bone Strength: What We Know—What We Need to Know
Thomas A. Lloyd, Ph.D., Professor of Clinical Epidemiology
Department of Health Evaluation Science
Hershey Medical Center, Pennsylvania State University College of Medicine

11:30 a.m. Discussion

12:00 p.m. Lunch

1:00 p.m. Glucocorticoid-Induced Osteoporosis and the Rheumatic Diseases
Nancy E. Lane, M.D., Associate Professor of Medicine
Division of Rheumatology, San Francisco General Hospital
University of California, San Francisco

1:15 p.m. Organ Transplantation and Other Secondary Causes of Osteoporosis
Elizabeth Shane, M.D., Professor of Clinical Medicine
Department of Medicine, College of Physicians and Surgeons
Columbia University

1:30 p.m. Discussion

Monday, March 27, 2000 (continued)

IV. Assessment of Osteoporosis

2:00 p.m. Needs and Opportunities in Assessment of Osteoporosis
C. Conrad Johnston, Jr., M.D., Distinguished Professor
School of Medicine, Indiana University

Evidence Report on the Diagnosis and Management of Osteoporosis

2:15 p.m. **Heidi D. Nelson, M.D., M.P.H., F.A.C.P.,** Assistant Professor of Internal Medicine and Medical Informatics and Outcomes Research
Oregon Health Sciences University

2:30 p.m. **Mark Helfand, M.D., M.P.H.**, Director, Evidence-Based Practice Center
Associate Professor of Internal Medicine and Medical Informatics and Outcomes Research, Oregon Health Sciences University

2:45 p.m. Discussion

Perspectives on the Evidence Report

3:15 p.m. Diagnostic and Intervention Thresholds in Osteoporosis
John A. Kanis, M.D., Professor
Center for Metabolic Bone Diseases
Medical School, University of Sheffield

3:30 p.m. Biochemical Markers of Bone Turnover
Douglas C. Bauer, M.D., Assistant Professor of Medicine
University of California, San Francisco

3:45 p.m. Use of T-Scores To Establish Comparable Diagnostic Categories for Bone Densitometers
Dennis M. Black, Ph.D., Professor
Department of Epidemiology and Biostatistics
University of California, San Francisco

4:00 p.m. Discussion

V. The Consequences of Osteoporosis

4:30 p.m. The Psychosocial Consequences of Osteoporosis
Deborah T. Gold, Ph.D., Associate Research Professor
Department of Psychology and Behavioral Science
Duke University Medical Center

Monday, March 27, 2000 (continued)

4:45 p.m. The Economic Impact of Osteoporosis
Anna Tosteson, Sc.D., Associate Professor of Medicine and Community and Family Medicine, Center for the Evaluative Clinical Sciences
Dartmouth Medical School

5:00 p.m. The Orthopedic Perspective on Consequences of Osteoporosis: The Need for Improved Treatment of Patients With Osteoporotic Fractures
Mark E. Bolander, M.D., Consultant
Division of Orthopedic Research, Department of Orthopedic Surgery
Mayo Clinic and Mayo Foundation

5:15 p.m. Discussion

6:00 p.m. Adjournment

Tuesday, March 28, 2000

7:30 a.m. Registration

VI. Osteoporosis Treatment I

8:30 a.m. Osteoporosis Treatment: Overview
John Paul Bilezikian, M.D., Professor of Medicine and Pharmacology
Chief, Division of Endocrinology, Department of Medicine
College of Physicians and Surgeons, Columbia University

8:45 a.m. Systematic Reviews of Osteoporosis Therapies
Gordon Guyatt, M.D., Professor
McMaster University

9:00 a.m. The Bisphosphonates
Clifford J. Rosen, M.D., Director
Maine Center for Osteoporosis Research, St. Joseph Hospital

9:15 a.m. Alternative Therapies for Treatment of Osteoporosis: SERMs and Phytoestrogens
Lorraine A. Fitzpatrick, M.D., Professor of Medicine
Endocrine Research Unit, Mayo Clinic and Mayo Foundation

9:30 a.m. Hormone Replacement Therapy for Postmenopausal Osteoporosis
Ann Cranney, M.D., M.Sc., Assistant Professor
Division of Rheumatology, Ottawa Hospital, Civic Campus

9:45 a.m. Discussion

Tuesday, March 28, 2000 (continued)

VII. Osteoporosis Treatment II

10:15 a.m. Treatment Effects of Nasal Spray Calcitonin in Postmenopausal Osteoporosis
Ethel S. Siris, M.D., Madeline C. Stabile Professor of Clinical Medicine
Department of Medicine, College of Physicians and Surgeons
Columbia University

10:30 a.m. Anabolic Agents for Osteoporosis
Robert Lindsay, M.D., Ph.D., Chief of Internal Medicine
Regional Bone Center, Helen Hayes Hospital

10:45 a.m. Combination Therapy for Osteoporosis
Robert R. Recker, M.D., Chief, Endocrinology Division
Director, Osteoporosis Research Center
Professor of Medicine
Creighton University School of Medicine

11:00 a.m. Physical Approaches to Fracture Prevention
Douglas P. Kiel, M.D., M.P.H., Associate Professor of Medicine
Harvard Medical School Division on Aging
Associate Director of Medical Research, Research and Training Institute
Hebrew Rehabilitation Center for Aged

11:15 a.m. Followup and Monitoring of Patients
Steven R. Cummings, M.D., Professor of Medicine, Epidemiology, and Biostatistics
Assistant Dean for Clinical Research
Department of Medicine
University of California, San Francisco

11:30 a.m. Discussion

VIII. Patient Perspective

12:30 p.m. **Katherine E. Sharp, M.P.H.**

12:40 p.m. **Jerome C. Donnelly, D.M.D.**

12:50 p.m. Adjournment

Wednesday, March 29, 2000

8:00 a.m.	Registration
8:45 a.m.	Remarks **Congresswoman Constance Morella**, 8th District, Maryland
9:00 a.m.	Presentation of Consensus Development Statement
9:30 a.m.	Public Discussion
11:00 a.m.	Panel Meets in Executive Session
1:00 p.m.	Press Conference
2:00 p.m.	Adjournment

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Abstracts

The following are abstracts of presentations to the NIH Consensus Development Conference on Osteoporosis Prevention, Diagnosis, and Therapy. They are designed for the use of panelists and participants in the conference and as a reference document for anyone interested in the conference deliberations. We are grateful to the authors, who have summarized their presentations and made them available in a timely fashion. Abstracts for the following presentations do not appear but are available in the conference packets.

Followup and Monitoring of Patients—Steven R. Cummings, M.D.

Osteoporosis in Men—Eric S. Orwoll, M.D.

Physical Approaches to Fracture Prevention—Douglas P. Kiel, M.D., M.P.H.

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The Pathophysiology of Osteoporosis

B. Lawrence Riggs, M.D.

The major proximate causes of osteoporotic fractures are decreased bone strength and increased bone trauma. Approximately 70 percent of the strength of bone is due to its mineral density. The remaining strength is accounted for by bone size (larger bones are stronger), bone shape, and the internal architecture of bone. The elderly have more trauma because of an increased propensity to fall and a reduced ability to break the impact of their fall.

Bone mineral density (BMD) late in life is determined by the former level of peak bone mass and the amount of bone that has been lost. Some estimate that peak bone mass and bone loss contribute equally to the variance in BMD among the elderly. As much as 70 percent of peak bone mass is genetically determined. Although associations have been reported between BMD and genetic polymorphisms for the vitamin D receptor, estrogen receptor, PTH receptor, TGFβ, and SP1 binding site for COLIA1, inconsistent results among studies suggest polygenic determinants. However, the identification of families in which high peak bone mass is inherited as an autosomal dominant trait suggests a role for as yet unidentified genes. The remaining variance in peak bone mass is largely accounted for by differences in nutritional factors, physical activity, onset of puberty and regularity of menses, and, in some persons, exposure to growth-arresting diseases or drugs.

After menopause, loss of the restraining effect of estrogen on bone cell activity (both osteoblasts and osteoclasts contain estrogen receptors) leads to a phase of accelerated bone loss lasting about 10 years that is associated with disproportionate cancellous bone loss and disrupted microarchitecture. A slow phase of loss of comparable proportions of cancellous and cortical bone then ensues and continues throughout life. This is associated with progressive impairment in intestinal calcium absorption and in renal calcium conservation that, unless compensated for by large increases in dietary calcium intake, leads to progressive secondary hyperparathyroidism. However, because of an age-related impairment in osteoblast function, the resultant increase in bone resorption is not offset by a compensatory increase in bone formation. There is now convincing evidence that loss of extraskeletal effects of estrogen on intestinal and renal calcium transport, rather than aging per se, is the major cause of slow bone loss in elderly women. Whether the age-related osteoblast defect is caused by estrogen deficiency, impaired production of growth factors, or both still is unclear.

Men with mutations of genes that regulate estrogen action have osteopenia. Serum biologically active estrogen (Bio-E) and testosterone (Bio-T) decline in aging men, but Bio-E correlates best with their level of BMD. Thus, estrogen deficiency may also contribute to the development of osteoporosis in men.

Finally, in both genders, sporadic factors affect some, but not other, members of the population and predispose them to additional bone loss and fractures. These factors include certain diseases, surgical procedures, and use of medications as well as behavioral risk factors such as tobacco use, alcohol abuse, low calcium intake, inactivity, and nutritional vitamin D deficiency, among others.

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Biomechanics of Osteoporotic Fractures

Mary L. Bouxsein, Ph.D.

Bone plays a vital role as a mineral reservoir and source of hematopoetic cells. However, its major functions are structural: to protect vital internal organs and to provide a framework that allows movement and locomotion. Bone is unique with respect to other structural materials in that it can undergo self-repair and can adapt its composition and structure in response to hormonal and mechanical stimuli.

From a mechanical viewpoint, osteoporotic fractures represent a structural failure of the skeleton wherein the load applied to a bone exceeds its ability to support that load. The load-bearing capacity of a bone depends primarily on the intrinsic *material* properties of the tissue that comprises the bone, the *structure* of the bone (the size, shape, and bone mass), and the specific *loading* conditions. Thus it is clear that factors related both to the loads applied to the bone and to its load-bearing capacity are important determinants of fracture risk (Figure 1).

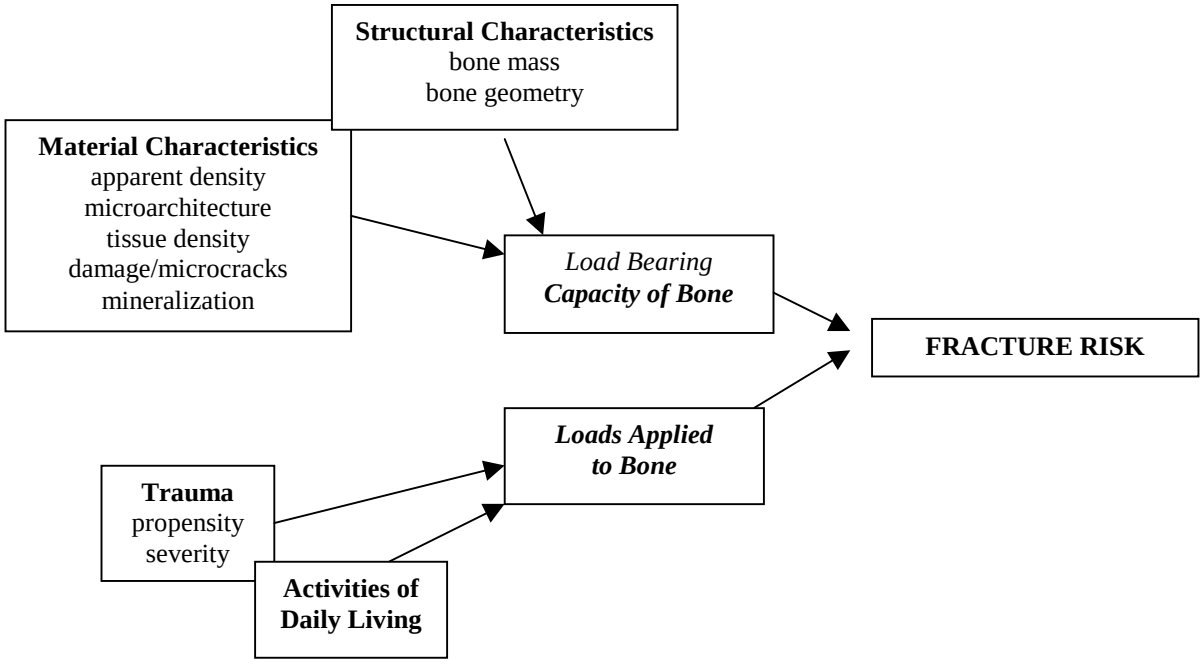

Figure 1. Determinants of fracture risk.

The intrinsic mechanical properties of both cortical and trabecular bone decrease dramatically with increasing age in men and women. These decreases in mechanical competence are due predominantly to age-related reductions in the apparent density (bone mass per unit volume) of cortical and trabecular bone, as 60 to 90 percent of the variability in trabecular and cortical bone strength is explained by apparent density. Moreover, the relationship between apparent density and trabecular bone strength is nonlinear (Carter, Hayes, 1977; Rice, Cowin, Bowman, 1988), whereby a decrease in the apparent density of trabecular bone leads to a

disproportionately larger reduction in bone strength. However, since 10 to 40 percent of the variability in bone strength remains unexplained by density, it is likely that other factors influence skeletal fragility. These factors may involve changes in trabecular architecture and in the bone tissue matrix itself. Changes in trabecular architecture, such as a decrease in the thickness and number of trabecular elements and the degree to which they are interconnected, accompany age-related declines in bone density. In the vertebral body, for example, preferential thinning and perforation of horizontally aligned trabecular elements substantially reduce the ability of the remaining vertical trabecular elements to support loads. Whereas these architectural features of trabecular bone are strongly correlated to bone density in "normal" nonpathologic bone (Compston, 1994; Goldstein, Goulet, McCubbrey, 1993), much less is known about the relationships among bone density, architecture, and bone strength in osteoporotic bone. Additional age-related changes in the properties of the bone tissue that may also contribute to increased skeletal fragility include alterations in the patterns of deposition or mineralization of bone matrix itself, an increase in osteonal remodeling, or an accumulation of microdamage. Bone microdamage, in the form of microcracks, accumulates with increasing age and appears to be greater in women than men (Mori, Harruf, Ambrosius, et al., 1997; Norman, Wang, 1997). However, the portion of the age-associated increase in fracture risk attributable to microdamage accumulation remains controversial (Burr, Forwood, Fyhrie, et al., 1997). These age-related decrements in bone density and mechanical properties may be partially offset by geometric rearrangements of the bone tissue, particularly in the long bones, that help to preserve the bone's ability to resist bending and torsional loads.

Arguably the most widely used measurement to diagnose osteoporosis and predict fracture risk is areal bone mineral density (BMD) by dual-energy X-ray absorptiometry. Although BMD measurements correlate strongly with the load-bearing capacity of the hip and spine, they are potentially limited in that they cannot measure trabecular and cortical bone compartments separately. Furthermore, they do not reflect trabecular architecture or other properties of the bone matrix that may be predictive of fracture risk. Thus, it may be useful to investigate new methodologies capable of assessing bone strength more accurately and precisely than the bone densitometry techniques that are used currently.

It is clear that bone strength plays an important role in fracture risk; therefore, investigations have focused primarily on methods to prevent bone loss and to restore bone to the osteopenic skeleton. However, alternative approaches for fracture prevention that are directed at reducing the loads applied to the skeleton may prove to be both effective and cost-efficient. Although much is known about the contribution of falls to hip fracture risk, little is know about the interactions between spinal loading and skeletal fragility in the etiology of vertebral fractures. In contrast to previously held beliefs that vertebral fractures are caused primarily by bending and lifting activities, there is increasing evidence that falls may also play a significant role in the etiology of vertebral fractures (Myers, Wilson, 1997). Thus, fracture prevention strategies should include prevention of falls, decreasing the severity of falls, and avoiding activities that generate high loads on skeletal sites at risk for fracture. For example, trochanteric padding systems designed to reduce the load applied to the hip during a fall have shown great potential for reducing fracture risk (Lauritzen, Peterson, Lund, 1993). Ultimately, fracture prevention may be best achieved by an educational program designed to limit high-risk activities in conjunction with interventions targeted at increasing bone strength and reducing loads applied to the skeleton.

Directions for Future Research

- Determine the relationships among bone density, architecture, microdamage, and turnover in normal and osteoporotic bone, and determine how these characteristics contribute to skeletal fragility.
- Improve existing and develop new noninvasive techniques for assessing skeletal fragility and for measuring the effects of therapeutic agents on skeletal fragility.
- Improve our understanding of the relative roles of skeletal fragility and skeletal loading in determination of fracture risk.

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Osteoporosis in 2000

L. Joseph Melton III, M.D.

Osteoporosis has been operationally defined as a bone mineral density (BMD) level more than 2.5 standard deviations (SD) below the mean for young normal white women (Kanis, Melton, Christiansen, et al., 1994). Because hip fractures represent the most important complication of osteoporosis and because proximal femur BMD has the strongest association with hip fracture risk, the focus has been on hip BMD. Data from the third National Health and Nutrition Examination Survey (NHANES III) reveal that 17 percent of postmenopausal white women have osteoporosis of the total hip (Looker, Orwoll, Johnston, et al., 1997). BMD measurements at other skeletal sites also predict fracture risk, as do ultrasound measurements, but the estimated prevalence of osteoporosis varies widely from one skeletal site or technology to another (Varney, Parker, Vincelette, et al., 1999). This relates partly to wider SD for less precise techniques but also to divergent patterns of age-related bone loss at different skeletal sites. An estimated 35 percent of postmenopausal white women have osteoporosis at either the hip, spine, or distal forearm, rising from 8 percent of women ages 50 to 59 to 82 percent of women age 80 and older (Melton, Atkinson, O'Connor, et al., 1998).

There is no consensus definition for osteoporosis in men or nonwhite women. However, NHANES data suggest that 12 percent of Mexican American and 8 percent of African American women in the United States have osteoporosis of the total hip, using the cutoff value for white women (Looker, Orwoll, Johnson, et al., 1997). Use of the same absolute cutoff value for defining osteoporosis in men produces an unrealistically low prevalence estimate, but sex-specific normal values result in an estimated 19 percent prevalence of any osteoporosis in men in Rochester, Minnesota (16 percent for total hip alone), which is consistent with the lifetime risk of osteoporotic fractures in men of approximately 13 percent (Melton, Atkinson, O'Connor, et al., 1998). Due to the lower young-normal mean and greater SD in NHANES, the prevalence of osteoporosis of the total hip was only 7 percent for non-Hispanic white men and even less for Hispanic and African American men (3 percent and 5 percent, respectively) (Looker, Orwoll, Johnson, et al., 1997). These discrepancies indicate a need for more robust normative data. It has become clear, however, that greater bone density in men compared with women, and in white women compared with Asian women, is partly an artifact of areal BMD (g/cm^2), since adjusting for scanned area does not account for wider bones also being deeper (Seeman, 1998). Body size adjustments reduce apparent differences in BMD among women of different races (Marcus, Greendale, Blunt, et al., 1994). Similarly, differences in bone density between men and women are reduced when overestimation of BMD in larger skeletons is corrected by assessing bone mineral apparent density (g/cm^3), although effects on osteoporosis prevalence vary.

Although we have a great deal of evidence about the size and identity of the population affected by osteoporosis, it is not altogether certain what these data mean. It is indisputable that almost all segments of the population are affected by osteoporosis to some degree and that the numbers affected will increase dramatically in the future as the population ages. What is needed is a more complete understanding of the bone density parameters that best represent skeletal fragility and increased fracture risk (Genant, Gordon, Jiang, et al., 1999). This would provide a

more appropriate basis for patient management and better estimates of the magnitude of the problem of involutional osteoporosis.

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Clinical Implications of Bone Density Variation Among Different Populations

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The known variation of bone mineral density (BMD) by gender and ethnicity, and the strong relationship of BMD to fracture risk, make BMD a useful epidemiologic tool. However, the optimal clinical application of BMD requires that a fundamentally different question be asked: Does the independent *contribution* of BMD to global fracture risk remain fairly consistent in different races and genders even though other risk factors may vary? This issue is important because if gender and race do not matter, then normal reference databases based on gender and race are unnecessary.

The primary evidence required to answer this question is derived from studies in which both genders, or two separate races, are studied simultaneously and prospectively, using identical methodology and adjusting for all covariates. Secondary or supportive evidence is derived from prospective studies that involved a single race or gender but attempted to adjust for other independent risk factors.

With regard to gender, four studies, conducted in Hawaii, Australia, Finland, and the Netherlands, examined men and women prospectively (Ross, Lombardi, Freedholm, 1999; Nguyen, Sambrook, Kelly, et al., 1993; Cheng, Suominen, Sakari-Rantala, et al., 1997; Lunt, Felsenberg, Reeve, et al., 1997). Each of these studies found a very similar, if not identical, relationship between BMD and absolute fracture incidence rates. Therefore, men and women with identical levels of bone density, *after* adjustment for age and other covariates, have the same absolute fracture risk. This is true for various bone density measurement sites in four different studies and at least two distinct racial groups. An in vitro study also found no gender-related difference in the relationship between volumetric density and compressive strength (Ebbesen, Thomsen, Beck-Nielsen, et al., 1999).

Secondary evidence has been summarized in a meta-analysis by Marshall, in which 11 different prospective studies were analyzed (Marshall, Johnell, Wedel, 1996). Mean relative risks for all studies were 1.95 for wrist, 1.9 for vertebral, and 2.06 for hip fractures. Therefore, irrespective of fracture site, BMD measurement site, or race, there is an approximate doubling of fracture risk for each standard deviation decrement of bone density. These data support the hypothesis that the independent relationship between bone density and fracture rate is very similar among different races and ethnic groups.

The implications of these findings for clinical practice are considerable: there is no need for innumerable normal reference databases (for each manufacturer, skeletal measurement site, technology, ethnic group, and both genders). Instead, BMD *and* other risk factors can be directly converted to absolute fracture rates, which can be expressed as 1-year, 5-year, or remaining lifetime fracture probabilities (RLFPs).

Besides its inherent simplicity, conversion of bone density levels to absolute fracture rates has another important advantage over the use of T-scores. It allows for the incorporation of

other important risk factors into the risk estimate, thus avoiding the misclassification of patients based on BMD alone. A final advantage of using absolute risk, as opposed to relative risks as represented by T-scores, is that all bone density measurement techniques and sites can be converted to the same outcome, allowing equivalent information to be derived from each test (Wasnich, 1997).

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Genetics of Age-Related Osteoporosis

Munro Peacock, M.D.

Age-related osteoporotic fracture is a complex disorder that arises stochastically from the interaction between trauma and decreased bone strength. The trauma is etiologically multifactorial, with environmental factors playing a dominant role. On the other hand, the components of bone strength (mass, structure, quality, and turnover) are highly heritable and can be readily quantified by noninvasive measurements. Thus, in seeking genes underlying age-related osteoporosis, our approach is to examine the quantitative phenotypes of bone strength for genetic linkage using a genome map of highly polymorphic microsatellite markers in a large population of premenopausal pairs of sisters (Koller, Rodriquez, Christian, et al., 1998; Koller, Econs, Rodriguez, et al., 1999).

Although single gene defects, such as occur in osteogenesis imperfecta, do give rise to osteoporotic fracture, it is generally considered that bone strength in the normal population is polygenic. Genetic mapping of phenotypes for age-related osteoporosis is limited by the inability to specify the model of inheritance. Thus, nonparametric model-independent methods, such as affected sib pair analysis, are used. Genetic linkage analysis uses the squared difference of the bone strength phenotype between the sib pair compared with the amount of genetic material shared identical by descent by the sib pair (Almasy, Blangero, 1998). This approach promises to be effective. We have obtained significant linkage of bone strength phenotypes in the normal population with a number of chromosomal sites and, in particular, with a site in linkage with familial disorders of both high (Johnson, Gong, Kimberling, et al., 1997) and low (Gong, Vikkula, Boon, et al., 1996) bone mass. This is in marked contrast to association studies with a "candidate" gene, which have yielded a plethora of positive associations of bone mass, and other apparently unrelated phenotypes, that cannot be reproduced outside the study populations.

The bone mass present in later life is determined both by peak bone mass and by age-related bone loss. Most heritability studies have focused on bone mass. Bone loss at the hip, the site of the most serious of the osteoporotic fractures, occurs soon after achieving peak mass but has not been studied in detail. Bone strength relates to skeletal size, with the largest individuals having the greatest bone strength. Differences in skeletal size account for some of the known differences in bone strength between the sexes and among races. The genetic basis for these differences is unknown, although our preliminary data in black and white sisters give similar heritabilities for bone strength phenotypes. Bone functions with muscle as the biomechanical unit. The consistent positive relationship between lean mass and bone strength suggests that skeletal mechanotransduction also has genetic regulators. Thus, it is important at this stage of our knowledge to study multiple phenotypes related to peak bone strength and bone loss since it is not yet clear which phenotypes are under primary genetic control.

Identification of the genes underlying bone strength will provide a number of advances in managing age-related osteoporosis. First, by identifying individuals at risk of low bone strength, it will allow early intervention with preventive measures. Second, because it is likely that the response to treatment is determined to some extent by genes regulating bone strength, it will

allow intervention therapy to be better tailored to the individual. Third, an understanding of the genetic regulation of bone strength will provide fundamental information on bone biology that will result in the development of novel treatments to optimize peak bone mass, prevent bone loss, and rebuild new bone.

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Nutrition—Beyond Calcium

Robert P. Heaney, M.D.

Bone, like all tissues, requires *total* nutrition for health. The extracellular phase requires protein, calcium (Ca), phosphorus (P), and possibly magnesium (Mg). Also, optimal functioning of the cells that lay down bone and monitor and maintain its integrity requires vitamins C, D, and K and the minerals copper (Cu), zinc (Zn), and manganese (Mn). Human or animal skeletal disorders have been reasonably well defined for deficiency states of each of the above nutrients. However, in this context, the relevant question is whether any of these nutrients or other diet features (besides calcium) contribute appreciably to human osteoporosis.

Protein is recognized as essential for building bone, but the current questions center on whether *excessive* protein intake contributes to the osteoporosis problem. Protein raises urine Ca by ~1 mg/g protein ingested, and since urine Ca is a more important determinant of Ca balance than diet Ca, this effect would be predicted to lead to negative bone balance. The action is mainly due to the S-containing amino acids (which are metabolized to sulfate). It is commonly, if erroneously, believed that animal proteins have a higher sulfur content than vegetable proteins; however, legumes average ~0.19 mmol S/g protein, and wheat and white rice ~0.31, with meats and dairy in between these extremes. Further, paleolithic protein intake—most of it of animal origin—is estimated to have provided up to 35 percent of total energy (at least 2 times its contribution to modern diets) (Cordain, Brand-Miller, Eaton, et al., in press). Skeletal health has manifestly been compatible with such intakes. The most likely explanation for these seeming discordances is that at low Ca intakes, such as prevail today, with Ca absorption efficiency close to maximal, the organism is not able to offset additional obligatory loss, such as induced by high protein intakes. At high Ca intakes, such as the paleolithic, absorption is down-regulated to prevent Ca intoxication, leaving ample potential to increase intestinal extraction efficiency. Finally, many elderly individuals have borderline protein malnutrition, a factor known to contribute to fracture risk. Protein supplements in hip fracture patients improve outcomes and retard age-related bone loss (Delmi, Rapin, Bengoa, et al., 1990; Schürch, Rizzoli, Slosman, et al., 1998). It seems likely, therefore, that if Ca and vitamin D intakes are adequate, protein effects on skeletal health are positive, not negative.

Most of what can be said of protein can also be said of sodium (Na). Every 100 mmol of Na raises urinary Ca by 0.5 to 1.5 mmol. In at least one study (Devine, Criddle, Dick, et al., 1995), age-related bone loss has been shown to be related to Na intake. While contemporary Na intakes are far higher than those of the paleolithic diet, ability to adapt is a direct function of Ca intake, just as it is for protein. Finally, the degree of reduction in Na intake required to protect the skeleton at contemporary Ca intakes is probably not realistically achievable. It is far easier to solve the problem by increasing Ca intake.

The issues surrounding phosphate are complex (Phosphorus, 1997). Phosphate constitutes 55 to 60 percent of bone mineral, and the diet must contain sufficient P to support bone growth. Moreover, bone mineralization and osteoblast activity will not occur normally if extracellular fluid (ECF) phosphate levels are low, irrespective of intake. (Indeed, relative hypophosphatemia is the common pathogenetic feature underlying most of the osteomalacias.)

Human P intake, often considered high, is actually low when adjusted to energy intake, relative to the diets of all laboratory animals (even factoring in cola consumption). Steady state, high P diets do not interfere with either Ca absorption or Ca balance, and while acute phosphate loads raise serum parathyroid hormone levels (PTH), at the same time they lower levels of bone resorption biomarkers, a seeming contradiction explained by osteoclast suppression by high ambient phosphate levels. Perhaps of more pertinence is whether *low* P intakes contribute to osteoporosis or limit therapeutic response. This question has not been directly tested. However, approximately 20 percent of older females ingest less than two-thirds of the RDA for P (Carroll, Abraham, Dresser, 1983) and may not, therefore, have access to sufficient phosphate to take full advantage of current bone-building regimens. Until this question is formally addressed, it may be prudent to employ one of the Ca phosphate salts (and/or dairy products) as the Ca source used with osteoporosis treatments.

A further question relates to a possibly deleterious effect of the proton load ingested in carbonated beverages that use phosphoric acid as the acidulant. Observational studies have noted an inverse relationship between carbonated beverage intake and bone mass and a direct relationship to fracture (Wyshak, Frisch, Albright, et al., 1989), but the available data make little distinction between beverages using phosphoric and citric acids as the acidulant. It is likely that milk displacement is a factor in such studies, since carbonated beverage and milk intakes tend to vary inversely. But whether the acid load has a negative skeletal effect in its own right at typical intakes has not been formally tested.

A related issue is the acid/alkali ash characteristic of the total diet. In general, vegetables produce an alkaline ash, meats an acid ash, and dairy foods a neutral ash. (The difference resides in their relative content of metabolizable and "hard" anions.) Substitution of bicarbonate or acetate for Cl^- in the diet lowers urinary Ca appreciably (Berkelhammer, Wood, Sitrin, 1988; Sebastian, Harris, Ottaway, et al., 1994). Thus, one would predict that an alkaline ash diet would favor bone. However, there is no direct evidence supporting this prediction, and three small studies of bone mass in vegetarians, in fact, showed lower bone mineral density (BMD) values than in omnivore controls. Finally, ethnographic studies of the diets of more than 1,200 primitive people with good bone health reveal typically very high meat intakes (Sebastian, Harris, Ottaway, et al., 1994). Therefore, it is unlikely that the animal/vegetable mix of contemporary diets (or their ash characteristic) contributes importantly to the clinical problem of osteoporosis.

Caffeine intake has also been linked in observational studies to osteoporosis (Heaney, in press, 2000a), but once again there is probably a milk-displacing effect of caffeine-containing beverages, which may be sufficient to explain the observed associations. Caffeine acutely increases urinary Ca but has no effect on 24-hour urine Ca, indicating a biphasic effect, probably reflecting caffeine's weak Na diuretic action. Caffeine does decrease Ca absorption, but the effect is very small and is easily offset by adding milk to one's coffee.

The trace minerals, particularly Cu, are of greater potential interest (Heaney, in press, 2000b). However, they are so little studied in this context that a role in human osteoporosis can be neither definitively included nor excluded. Cu is the cofactor for lysyl oxidase, an enzyme responsible for collagen cross-linking. Cu deficiency in experimental animals produces mechanically inferior bone and, in sheep, a lesion similar to human osteoporosis. There is

evidence of reduced numbers of extractable crosslinks in osteoporotic vertebral bone and at least one report of decreased serum Cu in patients with osteoporosis. Turnover of vertebral bone is rapid enough so that 5 to 10 years of bone remodeling under conditions of low Cu availability would be sufficient to replace highly crosslinked, normal bone matrix with a defective material. Therefore, there is enough plausibility about this mechanism to warrant detailed study.

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The Role of Calcium in the Prevention and Treatment of Osteoporosis

Bess Dawson-Hughes, M.D.

Calcium, along with vitamin D, is essential to support bone growth in children and bone preservation in young adults and to reduce fracture rates in older women. Supplementation with these nutrients is thought to lower fracture rates by at least two mechanisms: (1) by lowering the bone remodeling rate and (2) by lowering rates of bone loss from multiple skeletal sites. For instance, supplementation of healthy adults, age 65 and older, with 500 mg of calcium and 700 IU of vitamin D lowered mean serum levels of osteocalcin, a marker of bone turnover, by 9 percent in men and 14 percent in women (Dawson-Hughes, Harris, Krall, et al., 1997). The magnitude of these reductions was enough to reverse the rises in bone turnover that are seen with aging. The study subjects were consuming an average of 700 mg of calcium per day in their diets. In the study cited above, supplements significantly lowered rates of loss from the hip, spine, and total body in the men. Effects were somewhat smaller and significant only at the total body in the women. However, there are many other examples of supplemental calcium lowering rates of bone loss in postmenopausal women. The lowering of the remodeling rate accounts for some of the early (1-year) bone density gains that occur after initiating supplementation (known as the "bone remodeling transient"). However, cumulative gains in bone mineral density (BMD) have been noted at the femoral neck and total body (Aloia, Vaswani, Yeh, et al., 1994). Supplemental calcium is important in women who are taking estrogen to prevent or treat osteoporosis. A recent meta-analysis indicated that the BMD gains from estrogen replacement were significantly greater at all measured sites (the spine, hip, and forearm) in women with a mean calcium intake of 1,200 mg per day compared with women consuming an average of 600 mg per day (Nieves, Komar, Cosman, et al., 1998).

Information on the effect of added calcium, with and without vitamin D, on fracture rates has begun to emerge. The largest available study was conducted in more than 3,000 very elderly French women who resided in nursing homes (Chapuy, Arlot, Duboeuf, et al., 1992). Supplementation with 1,200 mg of calcium as calcium triphosphate along with 800 IU of vitamin D daily for 3 years significantly lowered hip and other nonvertebral fracture rates by about 30 percent. A meta-analysis of randomized trials of calcium supplements for the prevention of osteoporotic fractures in postmenopausal women indicated that calcium lowered fracture risk by 25 to 70 percent (Cumming, Nevitt, 1997). Few fracture data are available in men, but since supplements have similar effects on rates of bone remodeling and bone loss in men and women, it is likely that supplementation would lower fracture rates in men as it does in women. Finally, the antifracture efficacy of drugs approved recently for the treatment of osteoporosis has consistently been demonstrated in subjects (women) receiving supplemental calcium and often also added vitamin D. It should not be assumed that similar benefit would occur in post-menopausal women consuming less than the recommended intake of 1,200 mg per day of calcium (Standing Committee, 1997). In conclusion, calcium plays an essential role in both the prevention and treatment of osteoporosis.

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The Skeletal Effects of Exercise

Robert A. Marcus, M.D.

The notion that exercise benefits the skeleton finds support in the consequences of immobilization, the increased bone mineral density (BMD) of athletes, and the results of exercise trials. It is difficult to confirm strong associations between habitual physical activity and BMD for the general population. This reflects the nature of skeletal response, wherein effects of activity are greatest in people who are least active and attenuate progressively as habitual activity increases. Gains achieved by incremental exercise in active people are relatively meager. Training of young adults increases spine BMD by ~1.5 percent, with little response at the hip unless high impact forces, such as jumping, are also imposed. Nonetheless, changes achieved with training are less impressive than what might be predicted from observational studies of athletes, suggesting that some of the BMD difference between athletes and nonathletes represents ascertainment bias. Exercises that confer the greatest skeletal benefit involve relatively intense loading with high impact forces, such as gymnastics, in contrast to running and, in particular, to swimming, where impact forces are considerably lower or negligible. BMD returns quickly toward baseline levels when exercise training stops. Residual effects of past exercise in retired athletes appear to be small, if present. Thus, to deliver long-term skeletal benefits, exercise must be sustained over the lifespan. Childhood represents a unique period for achieving skeletal benefits. That is when vigorous exercise not only promotes BMD but may also initiate permanent beneficial changes in skeletal geometry.

One must consider these issues within the context of fracture prevention. BMD remains a laudable target, but given the modest response of BMD to training, exercise is not a panacea for bone fragility. For frail elders, fall prevention gains paramount importance. Muscle weakness is an important modifiable predictor of falls, so programs aimed at enhancing leg strength gain importance even without increasing BMD. Muscle strength and neuromuscular performance improve remarkably with training, even during the ninth decade. It is particularly encouraging to see these improvements with exercise programs that are less rigorous than those thought necessary for younger people. The primary goal of an exercise prescription for frail patients is safety; it should enhance the conduct of daily activities and minimize fracture risk. For patients with vertebral osteoporosis, the most harmful activity is back flexion. Conversely, gradually progressive exercise to strengthen back extensor muscles commonly reduces pain and improves activities of daily living.

The physical fitness of Americans continues to decline. Despite efforts to understand the skeletal effects of exercise at a molecular level, translation of new insights into measurable changes in fracture incidence will require investing similar effort into motivating a sedentary population to become more active.

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Peak Bone Mass—Peak Bone Strength: What We Know—What We Need To Know

Thomas A. Lloyd, Ph.D.

The peak bone mass (PBM) concept has been widely used in the past decade in our efforts to understand the development of osteoporosis and its related fractures. It is timely that we review how useful this model has been and consider other conceptual frameworks.

What We Know

Bone strength determines fracture risk. Bone strength is the result of bone material properties, bone microarchitecture, and bone macrogeometry. Thus, age-related loss of bone mass need not lead to a loss of bone strength. For example, during aging, bones have increases in diameter due to periosteal growth and decreases in cortical walls due to endosteal resorption. However, it is possible for aging bones to maintain or increase their section modulus values, thus preserving bone strength (Einhorn, 1992).

Bone mineral density (BMD) is a surrogate measure for bone strength. BMD measures only material properties. Thus, bones that may have identical BMDs but different diameters and cortical thicknesses will have different bone strengths (Beck, Ruff, Shaffer, et al.)

Peak hip BMD in females is reached by age 16. The average female gains 40 to 50 percent of her skeletal masses or approximately 1,000 g of bone mineral during adolescence. Our data and those of Martin and colleagues (1997) show that peak bone mineral accretion velocity in females occurs at the rate of about 240 g per year during ages 12 to 14. At this rate, approximately 650 mg bone mineral and, therefore, about 250 mg calcium are being added to the adolescent skeleton daily. However, the timing of peak bone mass achievement is site specific. The mechanical implications of this site-specific variation in bone accretion are not understood at present.

In females, peak hip BMD is achieved in late adolescence, usually by age 16, whereas peak lumbar spine and peak total body bone mineral density occur near age 20 (Zanchetta, Plotkin, Alvarez Filgueira, 1995; Lu, Briody, Ogle, et al., 1994). There is also evidence that the section modulus of the female femoral neck reaches its maximum value at age 20 and declines thereafter (Haapsalo, Kannus, Sievanen, et al., 1996).

Genetics are responsible for 80 percent of BMD. Since a 5 percent difference in PBM is believed to be associated with a 50 percent change in fracture risk in old age (Riggs, Melton, 1992), small changes in bone content and/or bone size early in life may have profound effects on fracture risk in later life.

Increased physical activity in adolescence is associated with increased hip BMD. The beneficial effects of weight-bearing exercise on BMD among adult women are well established. More recently, several studies, including our own, have demonstrated that increased

physical activity by children and teens is associated with increased adolescent bone gain (Morris, Naugton, Gibbs, et al., 1997; Lloyd, Chinchilli, Johnson-Rollings, in press). In the latter study at Pennsylvania State University College of Medicine (Penn State), the effect of exercise was specific for the proximal femur and did not affect total body bone measures.

Calcium intakes between 500 and 2,000 mg per day by adolescent women are not associated with PBM. Although calcium supplementation programs in childhood or adolescence generally lead to gains in bone mass and BMD, the effects do not persist. The evidence from multiyear prospective observational studies and from randomized trials do not show that calcium intake above 500 mg per day has a clinically important effect on bone mass or peak BMD (Lloyd, Johnson-Rollings, Chinchilli, in press; Welten, Kemper, Post, et al., 1994; Valmarki, Karkkainen, Lamberg-Allardt, et al., 1994).

Persistent hypoestrogenism in adolescence results in decreased PBM. Young women who miss 25 to 50 percent of their menses in adolescence will have lower PBM than their regularly menstruating peers (Drinkwater, Bruemner, Chestnut, 1990; Lloyd, Buchanan, Myers, 1988). Since prevalence estimates of oligomenorrhea among college women are 10 to 12 percent, the total number of American women so affected could be quite large.

A full-term pregnancy in adolescence is associated with significantly decreased peak hip BMD. The opportunity to collect pre- and postdelivery bone measures on young women who have babies between ages 16.5 to 19.5 is rare. Among the longitudinally studied Penn State cohort, there were five such cases. At age 20, their average hip BMD was 12 percent lower than that of matched controls (0.91 + 0.05 mg/cm^2 versus 1.04 + 0.03, p - 0.04). Learning whether they and additional teen mothers will gain hip BMD after age 20 is of clinical and biological importance.

Use of oral contraceptive pills (OCP) during adolescence does not affect PBM. While the benign effect of OCP use on bone measures in adult women has been well documented, the lack of an OCP effect on PBM has only recently been determined. The fact that OCPs function by suppression of ovarian production of sex steroids and decreases in PBM result from oligomenorrheic hypoestrogenism raises an important question as to what circulating levels of estrogens and androgens are required to support optimal adolescent bone growth.

What We Need To Know

- What noninvasive techniques can be developed to measure bone strength?
- Does increased PBM due to exercise or weight gain persist beyond age 20?
- Is decreased PBM due to teen pregnancy reversible?
- Will calcium supplementation have persistent bone benefits for adolescent women who have habitual intakes less than 500 mg per day? (According to the National Health and Nutrition Examination Survey [NHANES], about 25 percent of U.S. teen women have daily calcium intakes of less than 500 mg.)

- What are the thresholds for circulating levels of reproductive hormones that support acquisition of PBM?

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Glucocorticoid-Induced Osteoporosis and the Rheumatic Diseases

Nancy E. Lane, M.D.

Glucocorticoid-Induced Osteoporosis

Glucocorticoid-induced osteoporosis is the most common drug-induced cause of osteoporosis. Glucocorticoids reduce bone mass because they (1) reduce calcium absorption from the gastrointestinal tract and increase calcium loss in the urine, (2) reduce gonadal hormone production, and (3) decrease bone formation by suppressing osteoblast lifespan, numbers, and function. Trabecular (or cancellous) bone is most affected by glucocorticoids treatment, and chronic use results in a nearly 50 percent risk of osteoporotic fractures.

Glucocorticoid-induced osteoporosis can be both prevented and reversed. Any patient upon initiating glucocorticoid treatment of more than 7.5 mg per day of prednisone or its equivalent should have a bone mineral density test performed. This information will assist the physician and the patient in determining bone mass at the time glucocorticoids are initiated and provide a baseline measurement to monitor the efficacy of prescribed therapies. Studies have found that supplementation with calcium (1,500 mg per day by diet or supplement) and vitamin D_3 (400–800 IU per day) is important to reverse the negative calcium balance, reduce parathyroid hormone levels, and maintain bone mass in subjects on low daily doses of glucocorticoids. Also, antiresorptive agents (e.g., estrogen and bisphosphonates) are effective treatments to prevent glucocorticoid-induced bone loss. Therefore, preventive therapies should be initiated in subjects initiating glucocorticoid treatment who have risk factors for osteoporosis or in whom glucocorticoid therapy will continue for more than 3 months. In subjects chronically treated with glucocorticoids who have osteopenia (T-score <–1) as indicated by bone mass measurement, treatment with calcium, vitamin D_3, and antiresorptive therapy (bisphosphonates—alendronate and residronate) both prevent further bone loss and significantly reduce incident vertebral fracture risk.

Current treatments for glucocorticoid-induced bone loss correct the calcium balance and reduce further bone loss but do not reverse the primary lesion, the reduction in bone formation. Recently, osteoporotic postmenopausal women on chronic glucocorticoids and estrogen treated with daily subcutaneous injections of human parathyroid hormone 1-34 [hPTH(1-34)] for 1 year overrode the suppressive effects of glucocorticoids on bone formation and showed increased bone mass. Positive changes in spine bone mass in these women were 35 percent and 12 percent as measured by quantitative computed tomography (QCT) and dual-energy X-ray absorptiometry (DXA), respectively, while bone mass in the control group did not change. Therefore, anabolic agents like hPTH(1-34) or related compounds may be helpful for subjects who continue to fracture or lose bone mass on glucocorticoids despite appropriate therapy with calcium, vitamin D, and antiresorptive agents.

Osteoporosis and the Rheumatic Diseases

Individuals with inflammatory arthritis, especially rheumatoid arthritis, develop osteoporosis both at the site of the arthritis (juxta-articular osteoporosis and bone erosions) and in the central skeleton. The rheumatoid synovium is enriched with cells of the monocyte-macrophage lineage that can be induced to differentiate into osteoclasts with the stimulation of inflammatory cytokines from the synovium (IL-1, TNF, IL-6, IL-17, etc.). Recently, a new protein has been identified, osteoclast differentiation factor ODF (or osteoprotegerin ligand, OPGL, or RANK ligand), which is released by activated T cells in the bone marrow and rheumatoid synovium. When ODF interacts with its receptor NF-kB (RANK) on the surface of the osteoclast precursor, it leads to differentiation of the osteoclast and bone resorption. Another protein, osteoprotegerin (OPG), has been identified that controls the production of OPGL. Clinical studies are now under way to determine whether treatment with OPG will reduce bone loss in both the peripheral and central skeleton in individuals with rheumatoid arthritis.

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Organ Transplantation and Other Secondary Causes of Osteoporosis

Elizabeth Shane, M.D.

Definition

The term "primary osteoporosis" refers to the form of osteoporosis that is related to the normal phases of the human aging process, such as the bone loss that accompanies natural menopause or the normal aging process in all individuals, regardless of gender and race. In addition, a large and growing number of specific clinical disorders may contribute to the expected bone loss and fracture risk associated with menopause and aging. Secondary causes of osteoporosis include certain genetic diseases, such as osteogenesis imperfecta, hemochromatosis, and homocystinuria; hypogonadal states, such as hyperprolactinemia and anorexia nervosa; endocrine disorders, such as primary hyperparathyroidism, thyrotoxicosis, type 1 diabetes mellitus, and Cushing's syndrome; gastrointestinal disorders, including celiac disease, inflammatory bowel disease, primary biliary cirrhosis, and gastrectomy; connective tissue diseases, such as rheumatoid arthritis and ankylosing spondylitis; and diseases that involve the bone marrow, such as multiple myeloma, lymphoproliferative diseases, and systemic mastocytosis. In addition, many drugs, such as anticoagulants, immunosuppressive agents, anticonvulsants, thyroxine, chemotherapeutic drugs, and GnRH analogues, to name a few, are associated with alterations in bone remodeling that may lead to loss of bone mineral.

Scope of the Problem of Secondary Osteoporosis

It has been stated that 20 percent of postmenopausal women with osteoporosis have an identifiable secondary condition that may contribute to bone loss. The reported prevalence of secondary etiologies in men with osteoporosis is much higher (64 percent). The frequency of secondary causes in younger pre- and perimenopausal women is also high. Of 111 women younger than age 55 with low bone mass or osteoporosis evaluated at our center, 73 (66 percent) had identifiable causes of bone loss, of which estrogen deficiency was the most common.

Transplantation Osteoporosis: An Example of Medication-Induced Bone Loss

Candidates for kidney, kidney-pancreas, liver, lung, cardiac, and bone marrow transplantation have many risk factors for osteoporosis. The prevalence of osteoporosis and low bone mass before organ transplantation varies from approximately 80 percent in liver transplant candidates to 20 to 30 percent in kidney and bone marrow transplant candidates. After transplantation, there is exposure to high doses of glucocorticoids and cyclosporine A or tacrolimus, all of which have deleterious effects on the skeleton. The majority of patients experience rapid bone loss immediately after transplantation. Fragility fractures are common, particularly during the first posttransplant year. Bone loss may stop after the first 6 to 12 months or may continue at a much slower rate. The prevalence of vertebral fracture in organ transplant

recipients examined an average of 2 years after transplantation ranges from 10 percent in kidney transplant patients to 65 percent in those transplanted for primary biliary cirrhosis. Therefore, organ transplantation constitutes a significant risk factor for osteoporosis. Other common examples of secondary osteoporosis will be discussed.

Diagnostic Evaluation

The large number of diseases, conditions, and medications that can exacerbate age-related bone loss, as well as the high prevalence of secondary causes in men, young women, and even postmenopausal women with osteoporosis, makes it imperative that the clinician maintain a high level of suspicion when evaluating all patients with osteoporosis. Similarly, individuals with disorders associated with osteoporosis deserve to have a bone mass measurement so that osteoporosis can be diagnosed before fracture occurs.

A complete evaluation for secondary osteoporosis is costly and obviously cannot and should not be performed in everyone. Consideration should be given to whether the amount of bone loss is more severe than would be expected for the age, race, gender, and menopausal status of the individual (i.e., BMD Z-score >2 SD below the age-matched mean). Premenopausal and perimenopausal women with osteoporosis and men with osteoporosis warrant an intensive investigation. A complete history and physical examination are essential and may reveal one of the myriad causes of premature bone loss, such as hypogonadism, malabsorption, or Cushing's syndrome. Routine laboratory tests (complete blood count, chemistry profile, erythrocyte sedimentation rate, sensitive TSH, and 24-hour urinary calcium excretion) are usually normal in postmenopausal osteoporosis. Abnormal findings can provide clues to the presence of an underlying etiology and direct further investigations.

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Needs and Opportunities in Assessment of Osteoporosis

C. Conrad Johnston, Jr., M.D.

With an aging population, the consequences of osteoporosis-related fractures are becoming increasingly more common and costly. A few years ago, these fractures were considered to be due entirely to trauma. However, it has become apparent through studies of the biomechanics of fracture and through results of treatment with newer drugs that skeletal fragility is an important cause of fracture as well as trauma. We have learned that bone mass is an important contributor to bone fragility, but other factors, as yet poorly defined, must contribute as well. Since bone mass is a major factor contributing to fracture risk, it has been determined that osteoporosis can be diagnosed on the basis of low bone mass alone. Effective interventions have been developed that can prevent bone loss and reduce fracture incidence. How do we identify those in the population who would best be treated? How do we evaluate the rapidly accruing data on diagnosis of osteoporosis and choose the most soundly based evidence for presentation to clinicians and patients in a simple and usable form?

A review of current evidence for evaluating individuals with osteoporosis—or suspected osteoporosis—will be presented by the Oregon Health Sciences University Evidence-Based Practice Center. We know bone mass measurements can provide the risk of subsequent fracture, but what fractures are we most concerned about—hip, spine, wrist, or all fractures? Risk factors may differ for the different fracture syndromes. What is the optimal site to measure for risk assessment? Is this practical in the "real world"? What role do risk factors, especially those independent of bone mass, play in risk assessment? Is there a simple way to combine bone mass measurement and independent risk factors to select those at highest risk for intervention?

When the diagnosis of osteoporosis is made by bone mass measurement or the development of fractures, how diligently should we search for secondary causes? Are there specific tests that should be done on all individuals with this diagnosis, or should this depend on other factors (e.g., age)?

When therapy is undertaken, what outcome measurements, if any, should be monitored? Fracture in the individual will be difficult to follow. Will such monitoring affect adherence to therapy and assure a good outcome?

Data on evaluating risk of osteoporosis is rapidly accumulating, particularly in large ongoing clinical trials sponsored by industry. If data from these trials can be shared, we will have a powerful tool to evaluate measures that can lead to better criteria for intervention. Even with rapidly accumulating data, we still will have many unanswered questions, and we can only suggest to clinicians the best way to approach diagnosis. How these data can be presented in order to alter practice patterns remains unclear, but this must be resolved if individuals are to be evaluated in a cost-effective way and the proper outcome—reduced fractures—is achieved.

Evidence Report on the Diagnosis and Management of Osteoporosis

Heidi D. Nelson, M.D., M.P.H., F.A.C.P., and Mark Helfand, M.D., M.P.H.

The objective of this project was to conduct a systematic evidence review of the literature that will describe the effectiveness of various strategies for the diagnosis and management of postmenopausal women with osteoporosis as specified in six key questions. These questions were developed by members of the planning committee for the National Institute of Arthritis and Musculoskeletal and Skin Diseases consensus development conference on osteoporosis. The evidence report will be used as background material for the conference. The questions addressed by the report include the following:

1. What are the advantages and disadvantages of various bone mass measurement techniques at the different anatomic measurement sites for identifying women at high risk of fracture?

2. What is the role of markers of bone turnover for identifying women at risk of bone loss, guiding initial treatment decisions, or monitoring response to therapy?

3. What diagnostic or laboratory tests are appropriate for evaluating patients with osteoporosis, as determined by bone densitometry, quantitative ultrasound, or documented vertebral fractures?

4. Are bone mass measurements effective for monitoring response to treatment and for guiding decisions about changes in management?

5. What is the role of clinical risk factors, in conjunction with bone mass measurements, in identifying high-risk women and guiding initial treatment decisions?

6. Assuming consistent treatment approaches, what are the costs and cost-effectiveness of various diagnostic strategies for identifying women with osteoporosis?

The methodology of the evidence report follows specific conventions of the Evidence-Based Practice Centers, independent academic research groups contracting with the Agency for Healthcare Research and Quality to conduct such projects. The initial phase of the project involved assessment and refinement of the topic and key questions (posed by this consensus development conference and listed in the Introduction to this book) by consulting with local and national experts and stakeholders, refining the patient population, and developing a diagram that outlines the rationale and guides the literature search (Figure 1. Causal Pathway). Working with a medical librarian, investigators next developed literature search strategies and performed full MEDLINE searches. Additional references were obtained through secondarily referencing bibliographies of papers, consulting with experts, and searching for documents printed by sources such as industry, organizations, and governments. Investigators then developed inclusion and exclusion criteria for abstracts and papers and reviewed abstracts. Selected papers were then critically reviewed, and evidence tables were developed. Depending on the type of

data abstracted, a quantitative and/or qualitative summary of results was prepared. Finally, the draft evidence report was sent out for peer review and revision.

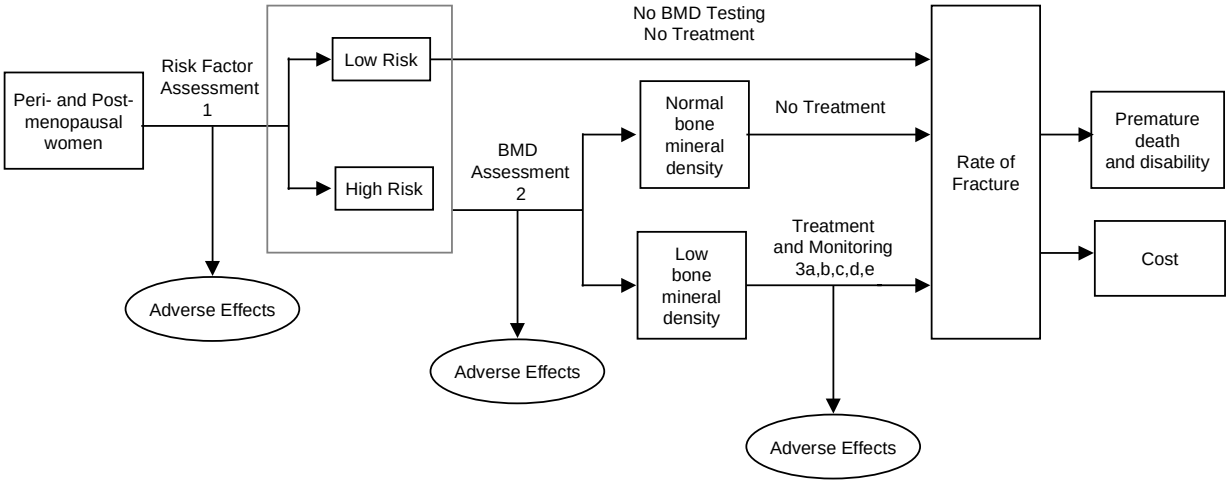

Figure 1. Osteoporosis diagnosis and management causal pathway.

Two questions in this project could not be addressed by the conventional literature search method. To determine the appropriate approach to further evaluate patients diagnosed with osteoporosis (Question 3), we compiled a table of recommendations from several professional organizations and authoritative texts, and we questioned practicing clinicians in several fields, asking them for their approaches. To assess the costs and cost-effectiveness of various diagnostic strategies (Question 6), we devised cost models based on assumptions supported by evidence obtained from the literature. These results, as well as those of the other questions, will be presented at the consensus development conference.

Diagnostic and Intervention Thresholds in Osteoporosis

John A. Kanis, M.D.

The burden of osteoporotic fracture is increasing worldwide because of the longevity of the population and, in some regions, because of increases in age and specific rates of fracture. With a better understanding of causation and treatment of osteoporosis, intervention strategies require development. Global strategies aimed at the population to decrease fracture risk, such as increases in calcium intake, are attractive but have not been tested. Their impact on fracture events is likely to be low. For this reason, greater attention has been devoted to high-risk strategies where segments of the community are identified for treatment. Such strategies require the development of diagnostic guidelines and determination of how these can be used to target segments of the population at high risk for osteoporotic fracture.

In 1994, the World Health Organization (WHO) proposed diagnostic guidelines for osteoporosis based on the measurement of bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) and the T-score. Osteoporosis is defined as a BMD value that is 2.5 standard deviations or more below the average value for young healthy women. More recently, criteria for men have been proposed utilizing the same threshold value for femoral neck BMD as that for women. The diagnostic threshold identifies approximately 15 to 20 percent of postmenopausal women as having osteoporosis when measurements using DXA are made at the spine or hip. Given an approximately linear loss of BMD with age, and because of the gaussian distribution of BMD values, the incidence of osteoporosis increases exponentially after the age of 50 years, as is also the case for many osteoporosis-related fractures.

Difficulties have arisen in applying diagnostic criteria because of the proliferation of measurement sites and the development of alternative technologies to assess BMD. Correlations of skeletal mass or density between sites or between techniques are less than optimal for predictive purposes due in part to the inherent inaccuracies in the technologies in question and to the biological variations that occur, particularly as a result of bone loss in the elderly. For this reason, measurements made at one site or with one technique can never have strong predictive value for measurement at an alternative site. Moreover, differences in rates of bone loss and in population variance mean that T-scores developed from one technique are not interchangeable with other sites or technologies. The same holds true in principle for hypertension where measurements made at the leg may differ substantially from measurements made at the arm. One solution would be to designate individuals with osteoporosis at the spine, but not at the hip, as having osteoporosis of the spine, rather than using the term “osteoporosis” alone. This seems unsatisfactory for a systemic disease and confuses the field still further in much the same way as hypertension of the leg would do. It appears more appropriate, therefore, to select a standardized site for the purposes of diagnosis, though not necessarily for risk assessment. It has recently been proposed that the hip should be the preferred site for diagnosis and that the use of the T-score in a diagnostic sense should be reserved for this site. Although there is not perfect concordance between bone density measurements in populations and fracture risk, it is recommended that international reference ranges be used (the NHANES III database) until further research tempers this view.

It is important to recognize that the assessment of BMD represents the assessment of a risk factor for osteoporotic fractures, albeit an important one. The gradient of risk between changes in bone mineral density and changes in fracture risk is insufficiently steep to recommend that density measurements can be used in whole population screening strategies targeted, for example, at the age of menopause. Under most reasonable assumptions, sensitivity of the technique is approximately 30 percent, which means that a large number of fractures would occur in those deemed not to be at risk. It is possible that screening strategies would be viable in the elderly where the absolute risk of fracture is high and the economic dividends are great, but this requires validation. Currently, case finding rather than screening is advocated. Two approaches to a case finding strategy have been adopted. In Europe, clinical risk factors are used to identify individuals in whom further assessment with BMD is justified. Individuals with osteoporosis are recommended for treatment. Since many individuals with clinical risk factors (e.g., family history of osteoporosis, smoking, prior fragility fracture) provide independent additive risks of fracture from that captured by BMD, segments of very high-risk populations identified for treatment are included. The guidelines are, however, conservative. In the United States, the approach has been to capitalize on the fact that clinical risk factors contribute to risk independently of BMD and that intervention thresholds should depend, therefore, on the presence or absence of such risk factors. Unfortunately, the recommendations derived by the National Osteoporosis Foundation border on the evangelical since they implicitly recommend screening at least in women older than age 65. Nonetheless, there is intuitive wisdom in the notion that if it is worthwhile to treat an individual with osteoporosis, say with a T-score of –2.5 standard deviations, then it is also worthwhile to give the same intervention to those with strong risk factors who may not exceed the threshold of the WHO criteria.

Thus, intervention thresholds should differ from treatment thresholds. The wide availability of “nondiagnostic” tests of bone mineral status and the many clinical risk factors permit assessments of risk, either in conjunction with diagnostic assessments or without their use. The consideration of other risk factors in conjunction with BMD assessment also improves the predictive value of the tests. For this reason, the future of osteoporosis should depend on the assessment of risk rather than the assessment of a T-score. It is desirable, therefore, to have measurements of all techniques expressed in units of risk, including clinical risk factors. Such approaches will ultimately enfranchise all technologies of predictive value. This will demand an examination of the independence of all these factors into suitable models that can be readily adapted for international rather than national use. It will also demand that clinicians and regulatory agencies accept the notion that a given risk of osteoporotic fracture provides an intervention threshold in much the same way as in the management of hyperlipidaemia, where intervention thresholds depend not only on lipid levels but also on other risk factors such as blood pressure and age.

Biochemical Markers of Bone Turnover

Douglas C. Bauer, M.D.

Bone remodeling is a physiologic process that begins with bone resorption, followed by bone formation. Although the mechanism is not well understood, resorption and formation are typically linked or coupled. Under some circumstances, such as estrogen deficiency in postmenopausal women, bone turnover is accelerated and resorption exceeds formation, resulting in bone loss.

The current status of the clinical usefulness of biochemical markers of bone turnover has been reviewed recently (Looker, Bauer, Chestnut, et al., in press) and is summarized below:

1. What are markers of bone turnover, and why might they be important?

Markers of bone turnover are biochemical substances found in the blood or urine, and measurement of these markers is a simple, noninvasive method to assess bone turnover. Some markers, such as bone-specific alkaline phosphatase (BSAP) and osteocalcin (OC), reflect bone formation, whereas others, such as pyridinolines (PYR) and type I collagen teleopeptides (CTX and NTX), reflect bone resorption.

The rate of bone turnover may be important for several reasons. High bone turnover states slightly favor bone resorption over bone formation, resulting in net bone loss. Theoretically, rapidly remodeling bone may be structurally compromised by the presence of many microscopic resorption pits.

The development of marker assays is rapidly improving, and commercial assays are widely available. Compared with measurements of bone mass, most marker measurements suffer from high interassay variability, which primarily reflects high biologic variability, particularly when measured in urine. This variability is summarized by the least significant change (LSC), defined as the minimum change that is unlikely to be chance variation. For example, the LSC for serum BSAP is reportedly 20 to 26 percent. Thus, if two measurements in an individual are obtained, only those that differ by 20 to 26 percent are likely to truly differ. The LCS for serum OC is 18 to 76 percent, while the reported LCS for urinary NTX is 43 to 93 percent.

2. Do markers predict fracture?

Numerous cross-sectional studies have demonstrated that marker levels and bone mass are not highly correlated ($r = 0.05$ to 0.15). However, a more important question is the ability of baseline marker levels to predict the risk fracture. Some, but not all, prospective cohort studies of older women have found that elevated markers of bone resorption are associated with an increased risk of hip fracture. For example, a large study of older women in France (Garnero, Hausherr, Chapuy, et al., 1996) found that urine CTX levels above the upper limit of normal for premenopausal women were associated with a twofold increase in hip fracture risk (RR 2.2, 95 percent CI 1.3, 3.6). This association was independent of bone mass, suggesting that high bone

turnover weakens bone strength by some other mechanism. Similar results have been reported for urinary PYR. These and other large studies in the United States have not found that markers of bone formation are related to hip fracture risk.

3. Do baseline markers predict bone loss?

Baseline marker levels are weakly associated with change in bone mass over time among untreated women as well as those treated with antiresorptive agents such as estrogen and bisphosphonates ($r = 0.1$ to 0.5). Thus, a single measurement of currently available markers is not useful to predict bone loss in postmenopausal women.

4. Do serial marker levels predict change in bone mass or fracture risk among treated women?

Within several months of starting antiresorptive therapy, marker levels fall by 20 to 60 percent. Prospective studies of estrogen- and bisphosphonate-treated women have found modest but statistically significant correlations between the initial fall in marker level and subsequent changes in bone mass over 1 to 3 years. For example, in one study of postmenopausal women treated with bisphosphonate for 3 years (Greenspan, Parker, Ferguson, et al., 1998), the correlation between the initial fall in urine NTX and subsequent increases in bone mass of the hip was very modest ($r = -0.28$, $p < 0.05$). Such low correlations are unlikely to be clinically useful. However, assuming that changes in bone mass do not fully reflect the beneficial effects of antiresorptive therapy, an extremely important unanswered question is the ability of serial marker measurements to predict fracture efficacy among treated women. To date, no prospective study has clearly demonstrated that the initial change in marker levels with antiresorptive therapy provides meaningful information about the likelihood of subsequent fracture. Although serial measurement of markers has been proposed to enhance compliance among treated women, there are no studies of this issue.

In summary, biochemical markers of bone turnover reflect rates of bone remodeling, and elevated levels of resorption markers may be associated with an increased risk of hip fracture. Currently available markers have not been shown to reliably predict bone mass or changes in bone mass. The ability of markers to predict fracture efficacy among treated women is unknown.

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Use of T-Scores To Establish Comparable Diagnostic Categories for Bone Densitometers

Dennis M. Black, Ph.D.

In 1992, the World Health Organization (WHO) Working Group on Osteoporosis proposed the bone mineral density (BMD) T-score concept (number of standard deviations below mean peak BMD) as an epidemiologic tool for comparing the prevalence of osteoporosis across different populations. Since that time, T-scores have become increasingly used for individual diagnosis of osteoporosis and for clinical decision-making; in fact, they serve as the basis for recent treatment recommendations from the National Osteoporosis Foundation (NOF).

Although T-scores were originally developed in terms of hip BMD, they have been applied to define diagnostic thresholds at other BMD sites and with other measures of bone strength, such as ultrasound. However, the comparability of populations defined by hip BMD versus other sites is unclear. If T-scores do not define comparable populations, then they cannot form the basis for the common definition of diagnostic thresholds. We propose that two dimensions of BMD comparability be considered:

1. The proportion of people with a BMD T-score below a given T-score cutpoint is the same, regardless of which device is used ("comparable prevalence").

2. Among those with a BMD T-score below the given T-score cutpoint, the fracture risk is similar ("comparable fracture risk").

To test the validity of either or both aspects of comparability, we compared the prevalence of osteoporosis (defined as T<–2.5) and the 5-year hip fracture risk among those with low BMD (T<–2.5) from various devices/techniques/sites. We used statistical models, including the assumption of a gaussian (normal) distribution of BMD at each age and a logistic relationship between BMD and fracture risk. Specific data parameters were derived from NHANES (Looker, Orwoll, Johnson, et al., 1997), manufacturers' normative databases and recent meta-analyses of the relationship of BMD and hip fracture risk (Marshall, Johnell, Wedel, 1996; Eddy, 1998). Table 1 shows that prevalence varies greatly, from 5.6 percent to 65.8 percent, with a similar variation in hip fracture risk.

We conclude that T-scores do not provide a rational basis for establishing comparable diagnostic thresholds.

Table 1. Prevalence of BMD T-score <–2.5 and hip fracture risk for some examples of devices/sites among 70-year-old women

Site	Manufacturer	RR/SD*	Prevalence <–2.5%	5-Year Risk (%) of Hip Fx
Femoral Neck	Lunar	2.6	20.7	6.5
	Hologic	2.6	24.5	5.9
Total Hip	Hologic	2.7	11.5	8.7
Spine	Hologic	1.6	34.8	3.7
Total Radius	Hologic	1.7	30.2	4.1
Os Calcis	Lunar (DXA)	2	5.6	8.0
	Hologic (Ultrasound)	2	8.7	7.0
	Lunar (Ultrasound)	2	22.8	5.1
Finger	Schick	1.6	15.7	4.6
Hand	Pronosco	2	65.8	3.2

* Relative risk of hip fracture per standard deviation decrease in BMD (Marshall, Johnell, Wedel, 1996; Eddy, 1998).

Over the past year, a committee that includes representatives from NOF, the American Society for Bone and Mineral Research (ASBMR), and the International Society for Clinical Densitometry (ISCD) has been working to establish a standard for comparability in diagnosis. We considered several possibilities, including setting thresholds yielding equal prevalence or equal fracture risk, since it seems impossible to achieve both. Based on our evaluations, we propose the following system for establishing comparable diagnostic cutpoints for all devices:

- Index levels of hip fracture risk will be based on the risk of hip fracture at each age among those with a BMD T-score <–2.5 at the femoral neck of the hip.
- Analogous ("risk-equivalent") cutpoints for other devices will be set such that the hip fracture risk among those below the cutpoints will be equal to the index risk.

The index risk and resulting cutpoints for two example devices are shown in Table 2.

Table 2. Comparable diagnostic cutpoints for two example sites

		Femoral neck (Hologic) RR = 2.6		Spine (Hologic) RR = 1.6		Calcaneal BMD (Lunar) RR = 2.0	
Age	5-yr Fx Risk (%)	Value	% Below	Value	% Below	Value	% Below
65–69	6.4	0.58	18	0.63	2	0.34	9
70–74	8.7	0.58	25	0.63	5	0.34	15
75–79	15.4	0.58	34	0.65	11	0.34	24
80–84	19.8	0.58	44	0.66	19	0.34	34
85–89	25.1	0.58	53	0.67	30	0.34	45

This initial proposal is limited to Caucasian women ages 65 and older, but future proposals will include other age and ethnic groups as well as men. In this example, we utilized a T-score value of −2.5, but a similar procedure can generate cutpoints for other T-score values.

These cutpoints can be derived for any device with data relating to hip fracture risk. Since BMD at the hip is most predictive of hip fracture risk, it results in the largest proportion of women with low BMD. Since other sites are less predictive, more extreme thresholds are required to achieve the same risk level. An important advantage of this procedure is that it can incorporate other risk factors or be adapted to future predictors of hip fracture risk (e.g., biochemical markers of bone metabolism). While a number of important issues remain, we believe this method provides a flexible framework for unified diagnoses in osteoporosis.

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The Psychosocial Consequences of Osteoporosis

Deborah T. Gold, Ph.D.

Osteoporosis results in a fragile skeleton and concomitant nontraumatic fractures that cause disability, deformity, and chronic pain. In recent years, substantial improvements have been made in the management of osteoporosis, and research on biomedical and clinical aspects of osteoporosis has increased substantially. However, behavioral and social science research about osteoporosis has received little attention. Given that the primary impact of osteoporosis on quality of life occurs in psychological and social arenas, we should strive to better understand these consequences.

The existing literature on the psychosocial consequences of osteoporosis is small. Studies of nonrepresentative samples of postmenopausal white women have found that persons with osteoporosis have restricted social integration and diminished self-concept; they also experience anxiety and depression. Obviously, the generalizability of these findings is limited, but they do provide some understanding of the quality-of-life impact of osteoporosis.

Studies in the late 1980s and early 1990s suggest that osteoporosis has negative social consequences. These effects are especially likely to occur in women with more than one clinically significant fracture. These fractures compromise physical activity and restrict participation in employment and family activities. The deformity and chronic pain caused by these vertebral fractures also restrict social activities. Changes in stature, back strength, and flexibility challenge the successful completion of critical social roles such as parent, grandparent, and worker. When these social roles cannot be engaged in, social relationships become problematic as well. Most of these relationships are based on reciprocity; these include family relationships, friendships, and work relationships. A loss of reciprocity because of osteoporosis can weaken or terminate those relationships. Losses such as these are devastating for the person with osteoporosis, especially at a time when emotional support is crucial.

In addition to its social impact, osteoporosis has psychological consequences. Again, these typically occur in the presence of symptomatic fractures. At the initial diagnosis of osteoporosis—and especially when the diagnosis results from a nontraumatic fracture—anxiety begins. Additional fractures, kyphosis, chronic pain, and functional impairment transform that anxiety into depression, perhaps the most significant mental health problem associated with osteoporosis. Increased stress and reduced self-esteem are also psychological outcomes of fractures and chronic pain. When people try to sustain their previous lifestyles in the face of osteoporosis, stress often results. Self-esteem, characteristically built on occupational success and physical appearance, decreases as people with fractures lose height, develop kyphosis, and become unable to complete common tasks such as lifting, bending, and stooping.

These studies have provided a direction for ongoing study of the sociobehavioral impact of osteoporosis on quality of life. However, almost no research has examined these outcomes in minority women, adolescents and premenopausal women, or men. Also ignored is the impact of osteopenia on quality of life. Further, because of the national research agenda, which emphasizes intervention, support for the necessary observational and descriptive studies in this

area is difficult to find. Instead of testing interventions with weak empirical underpinnings, investigators must concentrate on developing theories about the basic psychological and social consequences of this disabling disease.

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The Economic Impact of Osteoporosis

Anna Tosteson, Sc.D.

In recent decades, health care costs have increased dramatically, fueling interest in the economic consequences of disease and health care interventions. In the United States, the third National Health and Nutrition Examination Survey (NHANES III) estimated that 4 to 6 million women and 1 to 2 million men already have osteoporosis (Looker, Orwoll, Lindsay, et al., 1997). With the number of elderly in the United States projected to approximately double in the next 25 years (U.S. Census Bureau, 1996), an increasing number of men and women will be affected by osteoporosis. To address the economic aspects of osteoporosis, two forms of economic evaluation—cost-of-illness studies and cost-effectiveness analyses—are reviewed.

The primary objective in cost-of-illness studies is to estimate the total economic burden of disease in a defined population (Hodgson, Meiners, 1982). Osteoporosis cost-of-illness studies have focused on the economic impact of a subset of fractures with estimated annual costs ranging from $10.3 to $15.2 billion (Holbrook, Grazier, Kelsey, et al., 1984; Phillips, Fox, Jacobs, et al., 1988; Ray, Chan, Thamer, et al., 1997; Hoerger, Downs, Lakshmanan, et al., 1999) (Table 1). These prevalence-based estimates vary, in part because of the methods used and populations studied. While the low estimate of $10.3 billion reflected costs for only white women ages 45 and older (Phillips, Fox, Jacobs, et al., 1988), neither estimate included the indirect costs of morbidity and mortality that result from osteoporotic fracture (Ray, Chan, Thamer, et al., 1997). Indeed, most estimates include only a subset of the total direct medical costs of osteoporosis. Cost-of-illness estimates have not captured the additional direct medical costs of treatment among those who fractured or who are diagnosed with osteoporosis through bone mineral density screening. Thus, the true costs of osteoporosis have probably been underestimated.

Several patterns of resource utilization are evident from both osteoporosis cost-of-illness studies (Holbrook, Grazier, Kelsey, et al., 1984; Phillips, Fox, Jacobs, et al., 1988; Ray, Chan, Thamer, et al., 1997; Hoerger, Downs, Lakshmanan, et al., 1999) and model-based estimates of osteoporosis economic impact (Chrischilles, Shireman, Wallace, 1994). First, although hip fractures consistently comprise a large fraction of total osteoporotic fracture costs, a substantial proportion (estimated at 36.9 percent by Ray and colleagues) is attributable to nonhip fractures. To date, the health and economic consequences of nonhip fractures have received relatively little attention. Other fractures, which tend to occur earlier, may have measurable economic consequences when valued on the basis of lost work productivity (i.e., the human capital approach to estimating morbidity and mortality). Second, nursing home care accounts for an estimated 28 to 43 percent of the direct medical cost of osteoporotic fractures (Holbrook, Grazier, Kelsey, et al., 1984; Phillips, Fox, Jacobs, et al., 1988; Ray, Chan, Thamer, et al., 1997; Hoerger, Downs, Lakshmanan, et al., 1999; Chrischilles, Shireman, Wallace, 1994). This is consistent with hip fracture being a leading cause of hospitalization in the year in which individuals become catastrophically disabled (Ferruci, Guralnik, Pahor, et al., 1997); however, rates of fracture-attributable long-term institutionalization are not well documented. Third, in two recent studies (Ray, Chan, Thamer, et al., 1997; Randell, Sambrook, Nguyen, et al., 1995), expenditures in men accounted for approximately 20 percent of total costs, with expenditures in

men occurring at somewhat younger ages than in women (20 percent in men ages 45 to 64 compared with only 10 percent in women). Thus, the overall proportion of osteoporosis costs in men may increase when the economic consequences of osteoporosis-related morbidity and mortality are assessed. Finally, cost-of-illness studies can be informative regarding who bears the health care costs. A recent prevalence-based study of all health care use among U.S. women ages 45 years and older attributed 6.92 percent ($12.9 billion) of all annual direct medical expenditures to osteoporosis (Hoerger, Downs, Lakshmanan, et al., 1999). The largest proportion of these expenditures was born by Medicare (48 percent), with 24 percent paid by Medicaid, 11 percent by private insurers, and 17 percent by self/other payors.

To counter the increasing public health burden of osteoporosis, a growing number of interventions for osteoporosis prevention and treatment have been developed. Concern over the economic value of such interventions has promoted interest in another form of economic evaluation, cost-effectiveness analysis. In contrast to cost-of-illness studies, cost-effectiveness analyses (Gold, Siegel, Russell, et al., 1996) estimate the relative value of health interventions in an attempt to identify interventions that provide good value for the resources invested. These studies estimate the net change in cost relative to the net change in health. The recommended health outcome measure for such evaluations is the QALY (quality-adjusted life-year), which accounts for both duration and quality of life on a scale where 0 is worst imaginable health and 1 is best imaginable health (i.e., perfect health).

An up-to-date review of cost-effectiveness studies in osteoporosis is provided by Cranney and colleagues (Cranney, Welch, Lee, et al., 1999). The majority of these studies have assessed the cost-effectiveness of hormone replacement therapy. The effectiveness, cost, and lifetime cost-effectiveness of other interventions have not yet been thoroughly evaluated. Previous economic evaluations were hampered by a lack of data concerning the longitudinal cost consequences (both acute and long-term) of osteoporotic fractures and treatment interventions and appropriate data for estimating QALYs. In spite of these limitations, cost-effectiveness evaluations of osteoporosis prevention and treatment have been successful in identifying important determinants of cost-effectiveness, such as the period of treatment offset (Jonsson, Kanis, Dawson, et al., 1999) and rates of fracture-attributable long-term care utilization (Tosteson, Rosenthal, Melton, et al., 1990).

In summary, although the full economic consequences of osteoporosis have not yet been comprehensively evaluated, osteoporosis cost-of-illness studies have helped establish osteoporosis as a public health priority (Holbrook, Grazier, Kelsey, et al., 1984; Phillips, Fox, Jacobs, et al., 1988; Ray, Chan, Thamer, et al., 1997; Hoerger, Downs, Lakshmanan, et al., 1999). To prevent the morbidity, mortality, and economic costs that result from complications of osteoporosis, it is imperative that cost-effective approaches to osteoporosis prevention and treatment be identified for both men and women. To further the economic evaluation of interventions in osteoporosis, future studies should address the longitudinal impact of fractures on health care expenditures, indirect costs of morbidity and mortality, and health-related quality of life using QALY measures.

Table 1. Cost-of-illness studies addressing osteoporosis and/or fractures for the U.S. population

	Estimated Costs (1998 US$ billions)				Percent of Direct Costs			
	Study Year	Direct	Indirect[œ]	Total	Inpatient	Outpatient	Nursing Home	Other
Osteoporosis/Osteoporotic Fractures								
Holbrook et al., 1984[*]	1984	12.9	1.0	13.9	45	4	40	11
Phillips et al., 1988[†]	1986	10.3	--	--	55	4	41	--
Ray et al., 1997[‡]	1995	15.2	--	--	62	9	28	1
Hoerger et al., 1999[§]	1997	13.3	--	--	43	5	43	9
All Fractures								
Holbrook et al.,1984	1984	39.6	1.6	41.2	35	23	26	16
Praemer et al., 1992	1988	28.9	6.3	35.2	50	16	17	17
Pramer et al., 1999	1995	16.6	6.8	23.4	48	20	13	19

-- not estimated; [œ]estimated using the human capital approach
[*]Includes fractures of the vertebrae, upper femur, and forearm in men and women.
[†]Includes fractures of the vertebrae, upper femur, forearm, humerus, tibia, and fibula in women only.
[‡]Includes fractures of the vertebrae, upper femur, forearm, humerus, pelvis, skull, ribs, and other sites in men and women.
[§]Includes all fractures and diagnosis of osteoporosis in women ages 45 and older.

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The Orthopedic Perspective on Consequences of Osteoporosis: The Need for Improved Treatment of Patients With Osteoporotic Fractures

Mark E. Bolander, M.D.

The orthopedic treatment for patients with osteoporosis begins when efforts to prevent fracture have, unfortunately, failed. The goals of treatment are to provide immediate fracture stability and to promote healing—prerequisites for maximal functional recovery.

Efforts to stabilize the fracture frequently require surgery and internal fixation. Current orthopedic practice is to provide surgical stabilization for all hip fractures and the majority of Colles' fractures. The need for surgery and the specific surgical procedure are determined by radiographic assessment of fracture stability, coupled with a clinical estimate of the potential for healing. Although vertebral compression fractures are stable, fracture-related pain can be disabling. Two relatively new procedures, vertebroplasty and kyphoplasty, are successful in decreasing pain and restoring normal biomechanics in the spine. In addition to stable fixation, normal fracture healing depends on a vigorous healing response. A reparative callus, which includes cartilage and new bone, leads to "bone bridging" at the fracture site. Remodeling of this callus restores normal bone anatomy and function.

Complications after fracture are related to difficulties inherent in stabilizing fixation devices in weakened osteoporotic bone and to a decline in fracture healing capacity in the elderly. Reliable data on complications after fracture are not easily obtained from the literature, in part because of difficulties in evaluating fracture healing in human subjects. Nevertheless, most observers agree that at least 20 percent of patients with osteoporotic fractures, and in some studies as many as 40 percent, suffer complications including displacement, malunion, "cutting out" of the fixation device, nonunion, mechanical failure of the fixation device, and avascular necrosis.

Fracture healing may not be "normal" in patients with osteoporosis. Estrogen deficiency, known to impair osteoblast and chondrocyte function during growth, may also adversely impact function of these cells during fracture healing. Experimental studies show that fracture healing in animals is impaired by estrogen deficiency, while estrogen replacement restores normal healing.

Postfracture morbidity in osteoporotic patients significantly impairs functional recovery. As an example, approximately 50 percent of the elderly who were independently ambulatory before hip fracture were unable to walk without assistance after hip fracture, while approximately 25 percent of the elderly with hip fracture require long-term domiciliary care. Advanced age, poor medical condition, and fracture complications all contribute to postfracture morbidity. Evidence-based evaluations of fracture treatment are not frequently performed, however, and the relative contributions of prefracture conditions and postfracture complications to fracture-related morbidity are not known.

Techniques for stimulating fracture healing hold promise for improving fracture healing and possibly decreasing postfracture complications and morbidity in osteoporotic patients. Ultrasound, a form of mechanical stimulation, accelerates healing in patients with Colles' fractures. Although growth factors have not yet been shown to accelerate fracture healing in clinical studies, several, including fibroblast growth factors (FGFs), parathyroid hormone (PTH), and bone morphogenetic proteins (BMPs), hold promise for improving fracture healing. Treatment of estrogen deficiency may improve fracture healing and decrease the incidence of a second fracture, which is increased approximately 2.5-fold in patients with one osteoporotic fracture.

Summary

Considerable effort has been directed toward the diagnosis and treatment of osteoporosis, with the primary goal of fracture prevention. Less attention, however, has been directed to improving treatment of patients with osteoporosis once a fracture has occurred.

Treatment of osteoporosis-related fractures should include operative fixation of unstable fractures and radiographic evaluation to document healing and guide rehabilitation. Despite a consensus on appropriate fracture treatment, the available data show significant complication rates, unsatisfactory functional outcomes, and a high rate of subsequent fracture. There is, therefore, significant potential benefit to improving healing, decreasing complications, and treating underlying osteoporosis in these patients. Decreasing complications, accelerating healing, and decreasing subsequent fracture would support earlier rehabilitation, improved patient function, reduced resource utilization, and potentially reduced costs.

Osteoporosis Treatment: Overview

John Paul Bilezikian, M.D.

New and effective therapies for osteoporosis have helped to give new optimism to the fate of those suffering with this disease. In this section, these therapies will be reviewed. The intent of the presentations and associated discussion is to reach consensus on the available data for which the rules of evidence have been most rigorously applied. These rules of evidence depend on clinical trials that are conducted in such as way as to yield data that are "powered" to test the hypothesis and evaluated with the most modern statistical methodologies. Among a hierachy of evidence, the randomized clinical trial (RCT) is regarded to be the most revealing. Additionally, review of such well-conducted studies requires a methodology for which a systematic review (meta-analysis) can be applied across all such trials and from which valid conclusions can be drawn.

Estrogens have been the "gold standard" for the prevention and therapy of postmenopausal osteoporosis for decades. Older cross-sectional studies have seemed to provide a compelling profile of a therapy that not only prevents postmenopausal bone loss but also reduces the incidence of vertebral and hip fractures. Compromised somewhat by suboptimal experimental design, these studies have been followed by newer data based upon several prospective clinical trials that will be reviewed.

Despite general agreement that estrogen replacement therapy remains the "gold standard" for prevention and therapy of osteoporosis, real and perceived side effects have led to the development of a new class of estrogen-like agents, the selective estrogen receptor modulators (SERMs). SERMs share with estrogen some agonist properties, especially their antiresorptive effects on bone turnover. They are antiestrogenic for mammary tissue and the uterus. Raloxifene, an FDA-approved SERM for the prevention and therapy of osteoporosis, has been studied in several large-scale RCTs. A systematic review of these RCTs supports the hypothesis that raloxifene maintains bone mass and reduces vertebral fracture incidence.

The bisphosphonates represent an important nonhormonal approach to prevention and therapy of osteoporosis. Etidronate was the first bisphosphonate to be subjected to RCTs. Subsequently, alendronate, a more potent bisphosphonate, was approved by the FDA for osteoporosis prevention and therapy. Eleven RCTs for alendronate show a consistency in effects to increase bone mass and to reduce vertebral and nonvertebral fracture incidence. Risedronate, a bisphosphonate for which fewer RCTs are available for review, nevertheless also shows substantial increases in bone mass and reductions in vertebral and nonvertebral fractures. FDA approval of risedronate is expected soon.

Calcitonin continues to be a subject of scrutiny with regard to its antifracture efficacy. A recently concluded 5-year RCT, the PROOF study, was designed and powered to determine long-term efficacy and safety of nasal calcitonin. The results of this study, as well as issues regarding their interpretation, will be reviewed.

Although only antiresorptive drugs are currently available to treat osteoporosis, anabolic agents represent a new therapeutic horizon. Anabolic agents stimulate bone formation and, therefore, have the potential to improve bone mass to a much greater extent than the antiresorptives. Fluoride will clearly lead to marked increases in bone density, but its antifracture efficacy is still controversial. Parathyroid hormone, which has been known for years to be anabolic for cancellous bone, is showing promise in a number of studies. Finally, the potential use of combination therapy with antiresorptive and anabolic agents could well constitute the most promising approach to the therapy of osteoporosis.

The development of additional agents from the same classes currently available, as well as combination therapy and the anticipation of novel therapeutics for osteoporosis, augurs well for a field that just a few decades ago had little to offer in the way of effective therapy. It is this therapeutic optimism that fuels promise for greater advances in this decade.

Systematic Reviews of Osteoporosis Therapies

Gordon Guyatt, M.D.

Clinicians should make their treatment decisions on the basis of the best evidence of benefit and risk associated with alternative therapies. Randomized clinical trials (RCTs) focusing on patient-important end points are most likely to yield unbiased estimates. Estimates from a body of literature will remain biased unless investigators obtain all relevant data from RCTs and appropriately summarize the information.

The past decade has seen the development of a rigorous methodology for systematic review of data regarding treatment effectiveness. The process involves generating explicit and appropriate eligibility criteria, conducting a comprehensive search, assessing the methodological quality of the relevant studies, conducting appropriate pooled analyses (a meta-analysis), explaining heterogeneity of results across studies, and ensuring that each step is reproducible.

We have undertaken systematic reviews of the efficacy of alendronate, etidronate, residronate, calcium alone and in combination with vitamin D, calcitonin, raloxifene, and hormone replacement therapy in the prevention and treatment of osteoporosis in postmenopausal women. We estimated effects on bone density and vertebral and nonvertebral fractures demonstrated in RCTs.

There are advantages of pooling widely across patients (mild osteoporosis without fractures versus more severe osteoporosis with fractures), interventions, and outcomes. Estimates in subgroups are highly vulnerable to random error; wider pooling yields more robust estimates. Greater range of patient groups and variations in drug administration enhance generalizability of the results. We pooled widely and subsequently tested whether effects differed across patient groups, doses and durations of therapy, cointerventions, and trial methodological quality.

We undertook exhaustive searches, including obtaining unpublished data. For investigator-initiated trials, we sought information from authors with good success. For instance, of 16 authors of RCTs of calcium from whom we sought information, 13 complied. Many of our reviews were dependent on industry sponsors. To date, we have obtained complete information from the manufacturers of etidronate and alendronate.

Osteoporosis RCTs proved methodologically strong with one exception—high rates of loss to followup. For instance, of 13 RCTs of etidronate, 1 trial had a loss to followup of less than 1 percent, 5 trials from 5 to 20 percent, and the remaining 7 trials more than 20 percent; of 7 raloxifene trials with data available, 6 had loss to followup of more than 10 percent and the single largest trial more than 20 percent. We found no association between the extent of loss to followup and the magnitude of the treatment effect, suggesting that the high loss to followup may not have introduced important bias.

We summarized bone density results as the mean difference between treatment and control in the change from baseline to followup and the difference in fractures as a relative risk;

we calculated 95 percent confidence intervals for all estimates and tested each set of results for consistency across trials (heterogeneity). We sometimes found dose effects (larger fracture reductions at doses of 10 mg or greater for alendronate) and generally found larger effects on bone density after longer duration of therapy. We found similar effects of treatment on bone density in women with mild osteoporosis (prevention) and more advanced osteoporosis (treatment).

For most interventions, we were unable to exclude chance as an explanation of differences between treatment and control in the most important outcome, nonvertebral fractures, perhaps in part because of an inadequate number of events. For each of calcium (RR 0.86, 95 percent CI 0.43 to 1.72), calcium and vitamin D (RR 0.83, CI 0.62 to 1.12), etidronate (RR 0.99, 95 percent CI 0.69 to 1.42), and raloxifene (RR 0.91, 95 percent CI 0.78 to 1.06), pooled estimates showed weak trends favoring treatment.

The exception was alendronate, which at doses of 10 mg or more not only cut fracture rates in half (RR 0.51, 95 percent CI 0.38 to 0.69) but allowed interesting subgroup analyses. Alendronate's impact on traditional nonvertebral fractures, such as hip and forearm, thought to be "osteoporotic" (RR 0.46, 95 percent CI 0.32 to 0.66) was very similar to its impact on nonvertebral fractures, such as the foot, ankle, and toes (RR 0.57, 95 percent CI 0.32 to 1.02).

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The Bisphosphonates

Clifford J. Rosen, M.D.

The bisphosphonates are a class of drugs that bind avidly to calcium hydroxyapatite via their phosphate groups but are resistant to catalytic breakdown by skeletal pyrophosphatases. Their potency is determined by their side chains. Etidronate is a first-generation bisphosphonate administered cyclically in a 400 mg daily dose for 2 weeks every 3 months. There are 13 published randomized placebo-controlled trials (RPCTs) of etidronate, 8 prevention and 5 treatment. In the prevention and treatment studies, there were increases in spine bone mineral density (BMD) of 3 percent and 5 percent respectively, compared with placebo. Increases in femoral BMD were much smaller (1 to 3 percent). The largest RPCT included 400 postmenopausal women followed for 3 years, with an additional 4-year open-label study. The effects for all trials on vertebral fracture risk were relatively homogeneous: relative risk (RR) 0.63 (0.44 to 0.92). However, there was no statistical difference in the rate of nonvertebral fractures with etidronate: RR 0.99 (0.69 to 1.42). Etidronate is well tolerated, especially in respect to the gastrointestinal tract.

Alendronate has approximately 1,000 times the potency of etidronate and was approved for the treatment of postmenopausal osteoporosis in 1995. There are 11 RPCTs (treatment and prevention) of alendronate with various doses in more than 12,000 women. The Fracture Intervention Trial (FIT) was the largest (n = 6,000), and subjects were randomized to one of two arms on the basis of the presence or absence of prevalent fractures. Those women with low bone mass and prevalent fractures (n = 2,027) (FIT I) were randomized to placebo or 5 mg per day of alendronate for 2 years; the 5 mg per day group was switched to 10 mg per day for year 3. In FIT II (n = 4,432), women without prevalent fractures were randomized to one of three alendronate doses. For all prevention and treatment trials, there was a dose- and time-dependent effect on spine and hip BMD. The effect of alendronate on spine BMD was similar in all studies with doses greater than 5 mg per day, i.e., approximately 8-percent increase after 3 years compared with placebo. For hip BMD, there was a 5-percent increase and for the radius a 2-percent increase compared with placebo after 3 years. Doses of alendronate greater than 5 mg per day were associated with a pooled relative risk of 0.52 (0.42 to 0.65) for vertebral fractures. In the treatment trials (n = 5), there was a significant reduction (RR 0.49 [0.36 to 0.67]) in nonvertebral fractures including hip fractures, whereas in the one primary prevention study (FIT II), the relative risk was 0.79 (0.28 to 2.24) (p = 0.4 between treatment and prevention trials).

Although adverse gastrointestinal side effects with alendronate are uncommon in RPCTs, after marketing, there have been numerous such reports, the most prominent of which is erosive esophagitis. This may be due to the manner of drug administration, compliance with directions, use of other medications, placebo effects, or occult esophageal reflux disease. Notwithstanding, in the RPCTs, the relative risk of discontinuing medication because of adverse effects from 5 mg or greater of alendronate was 1.15 (95 percent CI 0.93 to 1.42).

Although there are only a few RPCTs for risedronate, there is a suggestion that this drug may have effects on bone mass and vertebral fracture risk similar to those of alendronate. The largest RPCT of risedronate in women with low bone mass and prevalent fractures included

more than 3,600 postmenopausal women (2,458 in North America and 1,200 in Europe) randomized to either 2.5 or 5 mg of risedronate or placebo for 3 years. In 2 smaller prevention trials, approximately 1,000 women with T-scores less than –2.0 were also randomized to 2.5 or 5 mg of risedronate. For 5 mg of residronate after 3 years, spine BMD increased 4.3 percent over placebo, hip BMD 2.8 percent, and radial BMD 1.6 percent. The relative risk for new vertebral fractures was 0.59 (0.43 to 0.82), and for nonvertebral fractures it was 0.60 (0.39 to 0.94). The number of new hip fractures in the two groups was not statistically different. Adverse gastrointestinal events were not different between treatment and placebo groups. In summary, risedronate has positive effects on BMD and vertebral fracture risk that approximate those observed with alendronate, although alendronate reduces the risk of new hip fractures while data for risedronate await further RPCTs.

Overall, there is strong evidence that the bisphosphonates, as a class, enhance bone mass at most skeletal sites and have a significant impact on vertebral fracture risk. Alendronate also has been clearly demonstrated to reduce the risk of nonvertebral fractures, including those of the hip, and, surprisingly, to lessen the risk of all types of fractures. Newer approaches to treating osteoporosis with the bisphosphonates are likely to include weekly oral dosing and intravenous administration several times per year.

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Alternative Therapies for Treatment of Osteoporosis: SERMs and Phytoestrogens

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Selective estrogen receptive modulators (SERMs) are nonhormonal agents that bind with high affinity to the estrogen receptor. These compounds exhibit estrogen-agonist and estrogen-antagonist effects on various target tissues. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) of one SERM, raloxifene, of at least 1-year duration. We identified 10 RCTs that met criteria, 4 concerned with treatment and 6 with prevention. Loss to followup was high in all trials: only one trial had a rate of less than 10 percent. We compared groups according to prevention (in which participants had bone density in the near normal range) versus treatment (where bone density was greater than 2 SD below peak bone mass). The results for bone mineral density (BMD) were pooled across all doses >30 mg but not across duration of therapy. There was a significant response in BMD at the lumbar spine, total body, and hip at 2 years: bone density increased by an average of approximately 2 percent in treated versus control patients. Larger effects were noted at 2 years; there was not a significant response to treatment at combined forearm, total body, and combined hip at 1 year.

Two trials reported morphometric vertebral fracture but used different criteria to define vertebral fracture. The majority of patients (7,705) were enrolled in the MORE (Multiple Outcomes of Raloxifene Evaluation) trial and given 60 or 120 mg/d of raloxifene or placebo. This trial showed a statistically significant reduction in vertebral fractures with a narrow confidence interval. At 60 mg/d of raloxifene, the relative risk for vertebral fracture was 0.7 (95 percent CI 0.5 to 0.8). Though the increases in bone density with raloxifene are smaller than seen with other antiresorptive therapy, the large effect on vertebral fractures suggests that raloxifene may have a positive effect on other aspects, such as bone architecture or quality. At the same time, therapy had no apparent effect on nonvertebral fractures: the pooled relative risk, consistent across both trials, was 0.91 (95 percent CI 0.78 to 1.06). Since the confidence interval shows that the results do not exclude a relative risk reduction of as much as 20 percent, further studies are indicated to assess the prevention of nonvertebral fractures by raloxifene.

A pooled estimate of the relative risk of discontinuing raloxifene as a result of adverse effects from the four trials using 30 mg of raloxifene or more was 1.14 (95 percent CI 1.00 to 1.30). Control group withdrawal rates varied from 9 to 14 percent. The relative risks from two trials for the side effects of breast pain based on data was 1.01, and the relative risk of leg cramps was 1.18. The relative risk of hot flashes from two trials was 1.57 (95 percent CI 1.37 to 1.81), and the control group rates of hot flashes varied from 6 to 27 percent, suggesting an absolute increase risk of hot flashes of approximately 3 to 15 percent.

Phytoestrogens are naturally occurring plant compounds that have estrogenic and/or antiestrogenic activity. They are present in many foodstuffs, and the main classes include the isoflavones, coumestans, and lignans. Evidence from animal species has demonstrated that the ingestion of high levels of phytoestrogens can produce adverse effects on reproductive end points. For osteoporosis, tentative evidence suggests that phytoestrogens may have positive

effects in maintaining bone density. Soy protein contains two isoflavones, genistein and daidzein, which have been studied in postmenopausal osteoporosis. Treatment for 1 year with soy protein containing 90 mg of isoflavones increased BMD of the lumbar spine compared with soy protein with the isoflavones removed. No differences were noted in hip BMD. A related synthetic phytoestrogen, ipriflavone, has been evaluated in clinical trials. In a study of 91 postmenopausal women, ipriflavone slightly increased bone density (spine and femoral neck) at 6 months compared with placebo, but not at 12 months. In a 2-year multicenter, double-blind, placebo-controlled clinical trial, a significant increase in BMD of the distal radius was noted at 12 and 18 months. However, only one-third of the subjects completed 18 months of study. Data on fracture incidence is currently not available with this compound. Longer RCTs with larger sample size and higher rates of followup are needed to evaluate the safety and efficacy of phytoestrogen-containing compounds.

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Hormone Replacement Therapy for Postmenopausal Osteoporosis

Ann Cranney, M.D., M.Sc.

Until recently, postmenopausal hormone replacement therapy (HRT) has been the main therapy for prevention of osteoporosis. HRT is not widely accepted by patients owing to concerns about the increased risk of breast cancer and side effects of breast tenderness and vaginal bleeding. Advantages of HRT include attenuation of hot flashes, lipid-lowering effects, and possible beneficial effects on cognition.

Numerous randomized control trials (RCTs) of short duration have been designed to evaluate bone density, which, because of its inconsistent relation to fracture reduction in randomized trials, we regard as a surrogate outcome. However, there is a paucity of trials with HRT designed to evaluate fractures as an end point. The evidence for fracture reduction with HRT comes primarily from observational trials; the magnitude of the reduction suggested is 50 percent for vertebral fractures and 25 to 50 percent for hip fractures with long-term use.

In our systematic review of HRT, we retrieved 57 published RCTs of HRT, which included 45 prevention and 12 treatment trials. We pooled across doses of HRT (opposed and unopposed) using a random effects model and then analyzed specific subgroups, according to dosage. Results from our pooled analyses revealed a consistent increase in bone density at all sites in the prevention and treatment trials. In the prevention trials, HRT relative to control increased bone density after 1 year by 4.86 percent (95 percent CI 3.70 to 6.02) (21 trials) at the lumbar spine. For the femoral neck, the pooled increase was 2.25 percent (95 percent CI 0.80 to 3.70) (5 trials), and for the forearm, it was 3.01 percent (95 percent CI 2.29 to 3.74) (20 trials). After 2 years, the pooled increase for the lumbar spine was 6.98 percent (95 percent CI 5.53 to 8.43) (17 trials), and for the forearm, it was 4.96 percent (95 percent CI 3.98 to 5.94) (15 trials).

For treatment trials at 1 year, the pooled increase for the lumbar spine bone mineral density was 7.04 (95 percent CI 4.70 to 9.36) (five trials), and for the forearm, it was 3.27 (95 percent CI 0.35 to 6.19) (two trials). There was little information on the effect of HRT on bone density of the femoral neck from the treatment trials.

We located five trials that included either vertebral or nonvertebral fractures as an end point. For vertebral fractures, the pooled relative risk was 0.57 (95 percent CI 0.28 to 1.16), and for nonvertebral fractures the relative risk was 0.50 (95 percent CI 0.27 to 0.94). The point estimates suggest an important reduction in vertebral and nonvertebral fractures consistent with the observational studies. However, the wide confidence intervals leave the true effect uncertain. Although there is evidence from RCTs that HRT increases bone density, at present the evidence for fracture reduction remains inconclusive. Future RCTs of varying HRT regimens that include fractures as the primary end point are recommended.

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Treatment Effects of Nasal Spray Calcitonin in Postmenopausal Osteoporosis

Ethel S. Siris, M.D.

Calcitonin is a polypeptide hormone that inhibits bone resorption. It has been used as a treatment for postmenopausal osteoporosis, initially in a formulation for subcutaneous injection and more recently as a nasal spray. In addition to its antiresorptive effects, it may have an anlagesic effect affording pain relief in the setting of vertebral compression fractures, as indicated by at least one well-designed study (Pun, Chan, 1989).

When the National Osteoporosis Foundation (NOF) reviewed the evidence for treatment effects of osteoporosis therapies (Eddy, Johnston, Cummings, et al., 1998), it was noted that studies with calcitonin included (at the time of publication) 18 randomized clinical trials involving more than 1,300 early and late postmenopausal women and using bone mineral density (BMD) effects as an end point. That review indicates that these studies—which varied greatly in terms of design, sample size, populations, duration of treatment, etc.—generally showed that injectable calcitonin decreases bone loss at the spine, either stabilizes or increases bone mass at the distal radius, and causes a dose-dependent increase in bone mass at the lumbar spine, femoral diaphysis, and proximal forearm. There were two trials evaluating fracture reduction with injectable calcitonin versus placebo, both relatively small and both indicating a reduction in vertebral fracture risk, but neither was viewed as having provided adequate statistical analysis of the data to support the conclusions that were reached.

A nasal spray formulation of calcitonin was developed in part to provide a simpler and more acceptable mode of administration. Several small studies with nasal spray calcitonin demonstrated modest but significant increases in spinal bone density compared with placebo (Overgaard, Riis, Christiansen, et al., 1989a; Overgaard, Riis, Christiansen, et al., 1989b). A randomized, double-blind, placebo-controlled study of 208 women (Overgaard, Riis, Christainsen, et al., 1992) indicated a 75-percent reduction in vertebral fracture rates after 2 years of nasal calcitonin and daily calcium, but there was felt to be a wide range of uncertainty regarding this figure by the NOF reviewers (Eddy, Johnston, Cummings, et al., 1998).

The PROOF study (Chestnut, Silverman, Andriano, et al., in press) is a recently concluded 5-year, placebo-controlled multicenter clinical trial designed to determine the long-term efficacy and safety of nasal spray salmon calcitonin in the prevention of vertebral fractures in osteoporotic postmenopausal women. (It was not designed to evaluate hip fracture reduction.) The study initially enrolled 1,255 postmenopausal women, all with lumbar spine BMD T-scores of at least –2 or lower, of whom 910 had one to five prevalent vertebral fractures (an entry criterion for all patients); 59 percent discontinued prematurely, equally distributed among dosages groups. Patients were randomly assigned in equivalent numbers to placebo or to 100, 200, or 400 u of nasal spray calcitonin daily. Spinal BMD increased significantly above placebo with all doses in years 1 and 2; by year 3, only the 400-u dose resulted in a BMD significantly higher than placebo; by year 5, the increases above baseline for placebo and the three ascending calcitonin doses were 0.54, 1.03, 1.15, and 1.54 percent, respectively. There was no treatment

effect on BMD with any dose at the femoral neck or trochanter. Compared with placebo, the 200- and 400-u doses significantly decreased serum carboxy-terminal collagen crosslinks (CTX) by 12.3 percent and 13.9 percent, respectively.

The primary end point of PROOF was reduction in vertebral fracture risk. At 5 years, there was a significant 33-percent reduction in the relative risk of developing a new vertebral fracture in the 200-u group (RR 0.67, 95 percent CI 0.47 to 0.997). There was no effect that differed from placebo with either 100 or 400 u. The number of hip fractures sustained was too few to make a meaningful analysis of any fracture reduction. The agent had excellent safety as anticipated.

The conclusions from PROOF suggest that this antiresorptive agent significantly reduced vertebral fracture risk by 33 percent at a dose of 200 u per day; this effect occurred with a very small increment in spinal bone density and a modest 12-percent reduction in the measured marker of bone resorption. The lack of a dose response, the high dropout rate, the apparent fracture reduction in the context of both very small increments in BMD and minimal reductions in bone resorption diminish to some degree the level of confidence in the fracture reduction results. The investigators have proposed that the decrease in vertebral fractures may have occurred as a consequence of improvements in bone quality not reflected by either BMD or conventional bone turnover assessment, and additional studies exploring this hypothesis are planned.

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Anabolic Agents for Osteoporosis

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Currently in the United States, all approved medicines for prevention and treatment of osteoporosis reduce both bone turnover and rate of loss of bone. Increases in bone density can usually be measured during the first 1 to 2 years of treatment and are assumed to be related to reduction in the size of the remodeling space, plus perhaps prolongation of the phase of secondary mineralization. None of these agents stimulates bone growth, and thus they are not anabolic. Only two agents have been demonstrated to stimulate bone formation—fluoride and parathyroid hormone (PTH).

Considerable basic and clinical information is available for fluoride, which in doses of 10 mg per day or greater produces marked increase in bone mass in many individuals. Data on fractures are more variable, with some studies suggesting a decrease in vertebral fracture risk, while others do not. The data on peripheral fractures are sparse, and there has been a suggestion that fluoride use may be associated with an increase in hip fracture risk. Animal and some human data suggest that the incorporation of fluoride into hydroxyapatite, the appearance of woven bone, and a defect in mineralization with fluoride use contribute to bone that is less mechanically sound.

PTH was first demonstrated to be anabolic in 1929 in a rodent model using PTH extract. Clinical studies were initiated in the 1970s when hPTH(1-34) was synthesized. Controlled clinical trials are only now beginning to be reported.

Considerable data from rodent and primate studies support the concept that PTH stimulates bone formation, particularly in cancellous bone and at the endocortical junction. Animal data from primates suggest that there is also an increase in cortical bone remodeling, with a consequent increase in cortical porosity. Biomechanical testing confirms a dose-dependent increase in vertebral strength and strength of the femoral neck in primates.

Several controlled clinical trials have reported marked increase in bone mass (measured by dual-energy X-ray absorptiometry [DXA]) in vertebrae of patients treated with either hPTH(1-34) or PTH(1-84). In essence, all studies demonstrate significant increases in bone density in the spine (up to 5 to 10 percent in 1 year, and 12 to 19 percent overall) by DXA, with larger changes measured by computed tomography. Smaller increases are seen at the hip (~5 percent) and in total body calcium. Some studies have shown a decline in BMD of hip or total body within the first year of treatment. Preliminary data suggest a dramatic effect on vertebral fractures, but there are no data as yet regarding peripheral fractures. One large Phase III study is expected to be reported soon.

Other agents have been investigated for their potential to be anabolic in the skeleton, including growth hormone and IGF, as well as androgenic steroids. None presently shows the potential of PTH.

Combination Therapy for Osteoporosis

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Clinical trials have demonstrated bone mass sparing and bone mass enhancing effects for at least two classes of pharmaceutical agents—hormone replacement therapy (HRT) and bisphosphonates, as well as two classes of supplements—calcium and vitamin D. Fluoride, in its various forms, and pituitary hormone (PTH) are also bone-active, though they remain under development and are not broadly available to clinicians. Clinicians and their patients have asked why not use these agents in combination, and indeed, many patients are now treated with various combinations in the absence of definitive data on their safety and efficacy. Questions include: Should combination therapies be considered? What is available evidence that they hold promise? What rationale exists for their use, and what approach might be considered in their development? The fact that clinicians and patients are already using combination therapies mandates that they be considered and makes it imperative that clinical science provide data to confirm their benefit and regimens that can be used by clinicians with confidence.

The rationale for combining therapy with available agents rests on the fact that these agents have different mechanisms of action; thus, their effects might be expected to be at least additive, if not synergistic. The approach to development is problematic because of the large number of possible drug combinations, regimens, and dosages. Not all possibilities can be realistically examined. However, one approach would be to select for testing a few regimens that seem to optimize for maximum safety and efficacy. Thus, for example, one might select a combination of low-dose continuous HRT (0.3 mg per day conjugated equine estrogens with 2.5 mg per day medroxyprogesterone) with prevention doses of alendronate (5 mg per day). This might also be augmented by supplements of calcium to 1,500 mg per day and vitamin D sufficient to raise serum levels of 25-hydroxy vitamin D to greater than 30 ng per ml. Other combinations also should be considered.

Several important studies now available are showing considerable promise. For example, Davis and colleagues showed annual bone gain of 0.75 percent, 0.25 percent, and 1.5 percent for HRT, calcium, and the combination, respectively. Komulainen and colleagues and Honkanen and colleagues demonstrated interactions between HRT, vitamin D, and calcium. Bone and colleagues demonstrated that spine BMD in women with low bone mass increased more with combined estrogen replacement therapy (ERT) and bisphosphonate than with either alone. Studies combining other bisphosphonates with HRT, and fluoride with HRT, have appeared, but with rather small numbers of subjects. These studies provide support for the notion that combination therapy with currently available agents holds promise for increased efficacy and/or reduced adverse effects.

It is important to design clinical trials with sufficient power to provide answers for clinicians and patients. Clinical studies of bisphosphonate/HRT regimens now under way will provide clinicians with data on regimens that hold this promise. However, more are needed. Sponsorship of trials of combination therapy will most likely come mostly from Government sources because of reluctance on the part of potential pharmaceutical sponsors to risk the reputation of their product in a combination trial.

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