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Osteoporosis Prevention, Diagnosis, and Therapy

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About the NIH Consensus Development Program

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NIH Consensus Statements are prepared by nonadvocate, non-Federal panels of experts, based on (1) presentations by investigators working in areas relevant to the consensus questions during a 2-day public session, (2) questions and statements from conference attendees during open discussion periods that are part of the public session, and (3) closed deliberations by the panel during the remainder of the second day and morning of the third. This statement is an independent report of the consensus panel and is not a policy statement of the NIH or the Federal Government.

Reference Information

For making bibliographic reference to this consensus statement, it is recommended that the following format be used, with or without source abbreviations, but without authorship attribution:


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Disclosure Statement

All of the panelists who participated in this conference and contributed to the writing of this consensus statement were identified as having no financial or scientific conflict of interest, and all signed conflict of interest forms attesting to this fact. Unlike the expert speakers who present scientific data at the conference, the individuals invited to participate on NIH consensus panels are selected specifically because they are not professionally identified with advocacy positions with respect to the conference topic or with research that could be used to answer any of the conference questions.
Abstract

Objective

The objective of this NIH Consensus Statement is to inform the biomedical research and clinical practice communities of the results of the NIH Consensus Development Conference on Osteoporosis Prevention, Diagnosis, and Therapy. The statement provides state-of-the-art information and presents the conclusions and recommendations of the consensus panel regarding these issues. In addition, the statement identifies those areas of study that deserve further investigation. The target audience of clinicians for this statement includes, but is not limited to, family practitioners, internists, gerontologists, orthopaedic surgeons, rheumatologists, obstetricians and gynecologists, and preventive medicine specialists.

Participants

A nonfederal, nonadvocate, 13-member panel representing the fields of internal medicine, family and community medicine, endocrinology, epidemiology, orthopaedic surgery, gerontology, rheumatology, obstetrics and gynecology, preventive medicine, and cell biology. In addition, 32 experts from these same fields presented data to the panel and a conference audience of approximately 700.

Evidence

The literature was searched using MEDLINE and an extensive bibliography of references was provided to the panel. Experts prepared abstracts for their conference presentations with relevant citations from the literature. Scientific evidence was given precedence over clinical anecdotal experience.

Consensus Process

The panel, answering predefined questions, developed their conclusions based on the scientific evidence presented in open forum and the scientific literature. The panel composed a draft statement, which was read in its entirety and circulated.
to the experts and the audience for comment. Thereafter, the panel resolved conflicting recommendations and released a revised statement at the end of the conference. The panel finalized the revisions within a few weeks after the conference. The draft statement was made available on the World Wide Web immediately following its release at the conference and was updated with the panel’s final revisions.

Conclusions

Osteoporosis occurs in all populations and at all ages. Though more prevalent in white postmenopausal females, it often goes unrecognized in other populations. Osteoporosis is a devastating disorder with significant physical, psychosocial, and financial consequences. The risks for osteoporosis, as reflected by low bone density, and the risks for fracture overlap but are not identical. More attention should be paid to skeletal health in persons with conditions known to be associated with secondary osteoporosis. Clinical risk factors have an important, but as yet poorly validated, role in determining who should have BMD measurement, in assessing risk of fracture, and in determining who should be treated. Adequate calcium and vitamin D intake are crucial to develop optimal peak bone mass and to preserve bone mass throughout life. Supplementation of these two components in bioavailable forms may be necessary in individuals who do not achieve recommended intake from dietary sources. Gonadal steroids are important determinants of peak and lifetime bone mass in men, women, and children. Regular exercise, especially resistance and high-impact activities, contributes to development of high peak bone mass and may reduce the risk of falls in older individuals. Assessment of bone mass, identification of fracture risk, and determination of who should be treated are the optimal goals when evaluating patients for osteoporosis. Fracture prevention is the primary goal in the treatment of patients with osteoporosis. Several treatments have been shown to reduce the risk of osteoporotic fractures. These include therapies that enhance bone mass and reduce risk or consequences of falls. Adults with vertebral, rib, hip, or distal forearm fractures should be evaluated for the presence of osteoporosis and given appropriate therapy.
Introduction

Osteoporosis is a major threat to 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 disorder.

Once thought to be a natural part of aging among women, osteoporosis is no longer considered age or gender-dependent. It is largely preventable due to the remarkable progress in the scientific understanding of its causes, diagnosis, and treatment. Optimization of bone health is a process that must occur throughout the lifespan in both males and females. Factors that influence bone health at all ages are essential to prevent osteoporosis and its devastating consequences.

The National Institutes of Health organized this 2-day conference to clarify the factors associated with prevention, diagnosis, and treatment of osteoporosis, and to present the latest information about this disease. After 1½ days of presentations and audience discussion, an independent, nonfederal consensus panel weighed the scientific evidence and drafted a statement that was presented to the audience on the third day. The consensus development panel’s statement addressed 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?

The lead organizations of this conference were the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the NIH Office of Medical Applications of Research. The conference was also supported 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).
What Is Osteoporosis and What Are Its Consequences?

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g., microfractures) and mineralization. A fracture occurs when a failure-inducing force (e.g., trauma) is applied to osteoporotic bone. Thus, osteoporosis is a significant risk factor for fracture, and a distinction between risk factors that affect bone metabolism and risk factors for fracture must be made.

It is important to acknowledge a common misperception that osteoporosis is always the result of bone loss. Bone loss commonly occurs as men and women age; however, an individual who does not reach optimal (i.e., peak) bone mass during childhood and adolescence may develop osteoporosis without the occurrence of accelerated bone loss. Hence sub-optimal bone growth in childhood and adolescence is as important as bone loss to the development of osteoporosis.

Currently there is no accurate measure of overall bone strength. Bone mineral density (BMD) is frequently used as a proxy measure and accounts for approximately 70 percent of bone strength. The World Health Organization (WHO) operationally defines osteoporosis as bone density 2.5 standard deviations below the mean for young white adult women. It is not clear how to apply this diagnostic criterion to men, children, and across ethnic groups. Because of the difficulty in accurate measurement and standardization between instruments and sites, controversy exists among experts regarding the continued use of this diagnostic criterion.
Osteoporosis can be further characterized as either primary or secondary. Primary osteoporosis can occur in both genders at all ages but often follows menopause in women and occurs later in life in men. In contrast, secondary osteoporosis is a result of medications, other conditions, or diseases. Examples include glucocorticoid-induced osteoporosis, hypogonadism, and celiac disease.

The consequences of osteoporosis include the financial, physical, and psychosocial, which significantly affect the individual as well as the family and community. An osteoporotic fracture is a tragic outcome of a traumatic event in the presence of compromised bone strength, and its incidence is increased by various other risk factors. Traumatic events can range from high-impact falls to normal lifting and bending. The incidence of fracture is high in individuals with osteoporosis and increases with age. The probability that a 50-year-old will have a hip fracture during his or her lifetime is 14 percent for a white female and 5 to 6 percent for a white male. The risk for African Americans is much lower at 6 percent and 3 percent for 50-year-old women and men, respectively. Osteoporotic fractures, particularly vertebral fractures, can be associated with chronic disabling pain. Nearly one-third of patients with hip fractures are discharged to nursing homes within the year following a fracture. Notably, one in five patients is no longer living 1 year after sustaining an osteoporotic hip fracture. Hip and vertebral fractures are a problem for women in their late 70s and 80s, wrist fractures are a problem in the late 50s to early 70s, and all other fractures (e.g., pelvic and rib) are a problem throughout postmenopausal years.

The impact of osteoporosis on other body systems, such as gastrointestinal, respiratory, genitourinary, and craniofacial, is acknowledged, but reliable prevalence rates are unknown.
Hip fracture has a profound impact on quality of life, as evidenced by findings that 80 percent of women older than 75 years preferred death to a bad hip fracture resulting in nursing home placement. However, little data exist on the relationship between fractures and psychological and social well-being. Other quality-of-life issues include adverse effects on physical health (impact of skeletal deformity) and financial resources. An osteoporotic fracture is associated with increased difficulty in activities of daily life, as only one-third of fracture patients regain pre-fracture level of function and one-third require nursing home placement. Fear, anxiety, and depression are frequently reported in women with established osteoporosis and such consequences are likely under-addressed when considering the overall impact of this condition.

Direct financial expenditures for treatment of osteoporotic fracture are estimated at $10 to $15 billion annually. A majority of these estimated costs are due to in-patient care but do not include the costs of treatment for individuals without a history of fractures, nor do they include the indirect costs of lost wages or productivity of either the individual or the caregiver. More needs to be learned about these indirect costs, which are considerable. Consequently, these figures significantly underestimate the true costs of osteoporosis.
How Do Risks Vary Among Different Segments of the Population?

Gender/Ethnicity

The prevalence of osteoporosis, and incidence of fracture, vary by gender and race/ethnicity. White postmenopausal women experience almost three-quarters of hip fractures and have the highest age-adjusted fracture incidence. Most of the information regarding diagnosis and treatment is derived from research on this population. However, women of other age, racial, and ethnic groups, and men and children, are also affected. Much of the difference in fracture rates among these groups appears to be explained by differences in peak bone mass and rate of bone loss; however, differences in bone geometry, frequency of falls, and prevalence of other risk factors appear to play a role as well.

Both men and women experience an age-related decline in BMD starting in midlife. Women experience more rapid bone loss in the early years following menopause, which places them at earlier risk for fractures. In men, hypogonadism is also an important risk factor. Men and perimenopausal women with osteoporosis more commonly have secondary causes for the bone loss than do postmenopausal women.

African-American women have higher bone mineral density than white non-Hispanic women throughout life, and experience lower hip fracture rates. Some Japanese women have lower peak BMD than white non-Hispanic women, but have a lower hip fracture rate; the reasons for which are not fully understood. Mexican American women have bone densities intermediate between those of white non-Hispanic women and African-American women. Limited available information on Native American women suggests they have lower BMD than white non-Hispanic women.
**Risk Factors**

Risks associated with low bone density are supported by good evidence, including large prospective studies. Predictors of low bone mass include female gender, increased age, estrogen deficiency, white race, low weight and body mass index (BMI), family history of osteoporosis, smoking, and history of prior fracture. Use of alcohol and caffeine-containing beverages is inconsistently associated with decreased bone mass. In contrast, some measures of physical function and activity have been associated with increased bone mass, including grip strength and current exercise. Levels of exercise in childhood and adolescence have an inconsistent relationship to BMD later in life. Late menarche, early menopause, and low endogenous estrogen levels are also associated with low BMD in several studies.

Although low BMD has been established as an important predictor of future fracture risk, the results of many studies indicate that clinical risk factors related to risk of fall also serve as important predictors of fracture. Fracture risk has been consistently associated with a history of falls, low physical function such as slow gait speed and decreased quadriceps strength, impaired cognition, impaired vision, and the presence of environmental hazards (e.g., throw rugs). Increased risk of a fracture with a fall includes a fall to the side and attributes of bone geometry, such as tallness, hip axis, and femur length. Some risks for fracture, such as age, a low BMI, and low levels of physical activity, probably affect fracture incidence through their effects on both bone density and propensity to fall and inability to absorb impact.

Results of studies of persons with osteoporotic fractures have led to the development of models of risk prediction, which incorporate clinical risk factors along with BMD measurements. Results from the Study of Osteoporotic Fractures (SOF), a large longitudinal study of postmenopausal, white non-Hispanic women, suggest that clinical risk factors can contribute greatly to fracture risk assessment. In this study,
14 clinical risk factors predictive of fracture were identified. The presence of five or more of these factors increased the rate of hip fracture for women in the highest tertile of BMD from 1.1 per 1,000 woman-years to 9.9 per 1,000 woman-years. Women in the lowest tertile of BMD with no other risk factors had a hip fracture rate of 2.6 per 1,000 woman-years as compared with 27.3 per 1,000 woman-years with five or more risk factors present. A second model, derived from the Rotterdam study, predicted hip fractures using a smaller number of variables, including gender, age, height, weight, use of a walking aid, and current smoking. However, these models have not been validated in a population different from that in which they were derived.

Secondary Osteoporosis

A large number of medical disorders are associated with osteoporosis and increased fracture risk. These can be organized into several categories: genetic disorders, hypogonadal states, endocrine disorders, gastrointestinal diseases, hematologic disorders, connective tissue disease, nutritional deficiencies, drugs, and a variety of other common serious chronic systemic disorders, such as congestive heart failure, end-stage renal disease, and alcoholism.

The distribution of the most common causes appears to differ by demographic group. Among men, 30 to 60 percent of osteoporosis is associated with secondary causes; with hypogonadism, glucocorticoids, and alcoholism the most common. In perimenopausal women, more than 50 percent is associated with secondary causes, and the most common causes are hypoestrogenemia, glucocorticoids, thyroid hormone excess, and anticonvulsant therapy. In postmenopausal women, the prevalence of secondary conditions is thought to be much lower, but the actual proportion is not known. In one study, hypercalciuria, hyperparathyroidism, and malabsorption were identified in a group of white postmenopausal osteoporotic women who had no history of conditions that cause bone loss. These data suggest that additional testing
of white postmenopausal women with osteoporosis may be indicated, but an appropriate or cost-effective evaluation strategy has not been determined.

Glucocorticoid use is the most common form of drug-related osteoporosis, and its long-term administration for disorders such as rheumatoid arthritis and chronic obstructive pulmonary disease is associated with a high rate of fracture. For example, in one study, a group of patients treated with 10 mg of prednisone for 20 weeks experienced an 8 percent loss of BMD in the spine. Some experts suggest that any patient who receives orally administered glucocorticoids (such as Prednisone) in a dose of 5 mg or more for longer than 2 months is at high risk for excessive bone loss.

People who have undergone organ transplant are at high risk for osteoporosis due to a variety of factors, including pretransplant organ failure and use of glucocorticoids after transplantation.

Hyperthyroidism is a well-described risk factor for osteoporosis. In addition, some studies have suggested that women taking thyroid replacement may also be at increased risk for excess bone loss, suggesting that careful regulation of thyroid replacement is important.

**Children and Adolescents**

Several groups of children and adolescents may be at risk for compromised bone health. Premature and low birth weight infants have lower-than-expected bone mass in the first few months of life, but the long-term implications are unknown.

Glucocorticoids are now commonly used for the treatment of a variety of common childhood inflammatory diseases, and the bone effects of this treatment need to be considered when steroid use is required chronically. The long-term effects on bone health of intermittent courses of systemic steroids or the chronic use of inhaled steroids, as are often used in asthma, are not well described.
Cystic fibrosis, celiac disease, and inflammatory bowel disease are examples of conditions associated with malabsorption and resultant osteopenia in some individuals. The osteoporosis of cystic fibrosis is also related to the frequent need for corticosteroids as well as to other undefined factors.

Hypogonadal states, characterized clinically by delayed menarche, oligomenorrhea, or amenorrhea, are relatively common in adolescent girls and young women. Settings in which these occur include strenuous athletic training, emotional stress, and low body weight. Failure to achieve peak bone mass, bone loss, and increased fracture rates have been shown in this group. Anorexia nervosa deserves special mention. Although hypogonadism is an important feature of the clinical picture, the profound undernutrition and nutrition-related factors are also critical. This latter point is evidenced, in part, by the failure of estrogen replacement to correct the bone loss.

**Residents of Long-Term Care Facilities**

Residents of nursing homes and other long-term care facilities are at particularly high risk of fracture. Most have low BMD and a high prevalence of other risk factors for fracture, including advanced age, poor physical function, low muscle strength, decreased cognition and high rates of dementia, poor nutrition, and, often, use of multiple medications.
What Factors Are Involved in Building and Maintaining Skeletal Health Throughout Life?

Growth in bone size and strength occurs during childhood, but bone accumulation is not completed until the third decade of life, after the cessation of linear growth. The bone mass attained early in life is perhaps the most important determinant of life-long skeletal health. Individuals with the highest peak bone mass after adolescence have the greatest protective advantage when the inexorable declines in bone density associated with increasing age, illness, and diminished sex-steroid production take their toll. Bone mass may be related not only to osteoporosis and fragility later in life but also to fractures in childhood and adolescence. Genetic factors exert a strong and perhaps predominant influence on peak bone mass, but physiological, environmental, and modifiable lifestyle factors can also play a significant role. Among these are adequate nutrition and body weight, exposure to sex hormones at puberty, and physical activity. Thus, maximizing bone mass early in life presents a critical opportunity to reduce the impact of bone loss related to aging. Childhood is also a critical time for the development of lifestyle habits conducive to maintaining good bone health throughout life. Cigarette smoking, which usually starts in adolescence, may have a deleterious effect on achieving bone mass.

Nutrition

Good nutrition is essential for normal growth. A balanced diet, adequate calories, and appropriate nutrients are the foundation for development of all tissues, including bone. Adequate and appropriate nutrition is important for all individuals, but not all follow a diet that is optimal for bone health. Supplementation of calcium and vitamin D may be necessary. In particular, excessive pursuit of thinness may affect adequate nutrition and bone health.
Calcium is the specific nutrient most important for attaining peak bone mass and for preventing and treating osteoporosis. Sufficient data exist to recommend specific dietary calcium intakes at various stages of life. Although the Institute of Medicine recommends calcium intakes of 800 mg/day for children ages 3 to 8 and 1,300 mg/day for children and adolescents ages 9 to 17, only about 25 percent of boys and 10 percent of girls ages 9 to 17 are estimated to meet these recommendations. Factors contributing to low calcium intakes are restriction of dairy products, a generally low level of fruit and vegetable consumption, and a high intake of low calcium beverages such as sodas. For older adults, calcium intake should be maintained at 1,000 to 1,500 mg/day, yet only about 50 to 60 percent of this population meets this recommendation.

Vitamin D is required for optimal calcium absorption and thus is also important for bone health. Most infants and young children in the United States have adequate vitamin D intake because of supplementation and fortification of milk. During adolescence, when consumption of dairy products decreases, vitamin D intake is less likely to be adequate, and this may adversely affect calcium absorption. A recommended vitamin D intake of 400 to 600 IU/day has been established for adults.

Other nutrients have been evaluated for their relation to bone health. High dietary protein, caffeine, phosphorus, and sodium can adversely affect calcium balance, but their effects appear not to be important in individuals with adequate calcium intakes.

**Exercise**

Regular physical activity has numerous health benefits for individuals of all ages. The specific effects of physical activity on bone health have been investigated in randomized clinical trials and observational studies. There is strong evidence that physical activity early in life contributes to higher peak bone mass. Some evidence indicates that resistance and high impact exercise are likely the most beneficial. Exercise during the middle years of life has numerous health benefits, but there are few studies on the effects of exercise on BMD.
Exercise during the later years, in the presence of adequate calcium and vitamin D intake, probably has a modest effect on slowing the decline in BMD. It is clear that exercise late in life, even beyond 90 years of age, can increase muscle mass and strength twofold or more in frail individuals. There is convincing evidence that exercise in elderly persons also improves function and delays loss of independence and thus contributes to quality of life. Randomized clinical trials of exercise have been shown to reduce the risk of falls by approximately 25 percent, but there is no experimental evidence that exercise affects fracture rates. It also is possible that regular exercisers might fall differently and thereby reduce the risk of fracture due to falls, but this hypothesis requires testing.

Gonadal Steroids

Sex steroids secreted during puberty substantially increase BMD and peak bone mass. Gonadal steroids influence skeletal health throughout life in both women and men. In adolescents and young women, sustained production of estrogens is essential for the maintenance of bone mass. Reduction in estrogen production with menopause is the major cause of loss of BMD during later life. Timing of menarche, absent or infrequent menstrual cycles, and the timing of menopause influence both the attainment of peak bone mass and the preservation of BMD. Testosterone production in adolescent boys and men is similarly important in achieving and maintaining maximal bone mass. Estrogens have also been implicated in the growth and maturation of the male skeleton. Pathologic delay in the onset of puberty is a risk factor for diminished bone mass in men. Disorders that result in hypogonadism in adult men result in osteoporosis.
Growth Hormone and Body Composition

Growth hormone and insulin-like growth factor-I, which are maximally secreted during puberty, continue to play a role in the acquisition and maintenance of bone mass and the determination of body composition into adulthood. Growth hormone deficiency is associated with a decrease in BMD. Children and youth with low BMI are likely to attain lower-than-average peak bone mass. Although there is a direct association between BMI and bone mass throughout the adult years, it is not known whether the association between body composition and bone mass is due to hormones, nutritional factors, higher impact during weight-bearing activities, or other factors. There are several observational studies of fractures in older persons that show an inverse relationship between fracture rates and BMI.
What Is the Optimal Evaluation and Treatment of Osteoporosis and Fractures?

The goals for the evaluation of patients at risk for osteoporosis are to establish the diagnosis of osteoporosis on the basis of assessment of bone mass, to establish the fracture risk, and to make decisions regarding the needs for instituting therapy. A history and physical examination are essential in evaluating fracture risks and should include assessment for loss of height and change in posture. Laboratory evaluation for secondary causes of osteoporosis should be considered when osteoporosis is diagnosed. The most commonly used measurement to diagnose osteoporosis and predict fracture risk is based on assessment of BMD which is principally determined by the mineral content of bone. BMD measurements have been shown to correlate strongly with load-bearing capacity of the hip and spine and with the risk of fracture. Several different techniques have been developed to assess BMD at multiple skeletal sites including the peripheral skeleton, hip, and spine. The World Health Organization (WHO) has selected BMD measurements to establish criteria for the diagnosis of osteoporosis. A T-score is defined as the number of standard deviations (SD) above or below the average BMD value for young healthy white women. This should be distinguished from a Z-score, which is defined as the number of SD above or below the average BMD for age- and gender-matched controls. According to the WHO definition, osteoporosis is present when the T-score is at least minus 2.5 SD. Although T-scores were based originally on assessment of BMD at the hip by dual-energy X-ray absorptiometry (DXA), they have been applied to define diagnostic thresholds at other skeletal sites and for other technologies. Experts have expressed concern that this approach may not produce comparable data between sites and techniques. Of the various sampling sites, measurements of BMD made at the hip predict hip fracture better than measurements made at other sites while BMD measurement at the spine predicts spine fracture better than measures at other sites.
Newer measures of bone strength, such as ultrasound, have been introduced. Recent prospective studies using quantitative ultrasound (QUS) of the heel have predicted hip fracture and all nonvertebral fractures nearly as well as DXA at the femoral neck. QUS and DXA at the femoral neck provide independent information about fracture risk, and both of these tests predict hip fracture risk better than DXA at the lumbar spine. In general, clinical trials of pharmacologic therapies have utilized DXA, rather than QUS, for entry criterion for studies, and there is uncertainty regarding whether the results of these trials can be generalized to patients identified by QUS to have high risk of fracture.

Over the past year, several professional organizations have been working on establishing a standard of comparability of different devices and sites for assessing fracture risk. With this approach, measurements derived from any device or site could be standardized to predict hip fracture risk. However, the values obtained from different instruments cannot be used to predict comparable levels in bone mass. Limitations in precision and low correlation among different techniques will require appropriate validation before this approach can be applied to different skeletal sites and to different age groups.

It has been suggested that the diagnosis and treatment of osteoporosis should depend on risk-based assessment rather than solely on the assessment of a T-score. Consideration of risk factors in conjunction with BMD will likely improve the ability to predict fracture risk. This approach needs to be validated in prospective studies and tested in appropriate randomized clinical trials.

In addition to the effects of bone mass, bone microarchitecture, and macrogeometry, bone strength is also affected by the rate of bone remodeling. Bone remodeling can be assessed by the measurement of surrogate markers of bone turnover in the blood or urine. These markers include bone-specific alkaline phosphatase and osteocalcin, which are indices of bone formation, and the urinary levels of pyridinoline and deoxypyridinoline and serum and urine levels of type I collagen telopeptides (CTX and NTX), which are indices
of bone resorption. The level of these markers may identify changes in bone remodeling within a relatively short time interval (several days to months) before changes in BMD can be detected. However, according to available data, marker levels do not predict bone mass or fracture risk and are only weakly associated with changes in bone mass. Therefore, they are of limited utility in the clinical evaluation of individual patients. Despite these limitations, markers have been shown in research studies to correlate with changes in indices of bone remodeling and may provide insights into mechanisms of bone loss.

Who Should Be Evaluated?

The value of bone density in predicting fracture risk is established, and there is general consensus that bone density measurement should be considered in patients receiving glucocorticoid therapy for 2 months or more and patients with other conditions that place them at high risk for osteoporotic fracture. However, the value of universal screening, especially in perimenopausal women, has not been established. There are several unknown factors with this approach. First, the number of women evaluated and treated would need to be high in order to prevent a single fracture. For example, in white women aged 50–59, an estimated 750 BMD tests would be required to prevent just one hip or vertebral fracture over a 5-year period of treatment. Second, the value has not been established for the common practice of beginning preventive drug therapy in the perimenopausal period for the purpose of preventing fractures later in life.

Until there is good evidence to support the cost-effectiveness of routine screening, or the efficacy of early initiation of preventive drugs, an individualized approach is recommended. A bone density measurement should be considered when it will help the patient decide whether to institute treatment to prevent osteoporotic fracture. In the future, a combination of risk factor evaluation and bone density measurements may increase the ability to predict fracture risk and help with treatment decisions. Until assessment by randomized clinical
trials is conducted, individual decisions regarding screening could be informed by the preliminary evidence that the risk for fracture increases with age, and with an increased number of additional risk factors.

**What Are the Effective Medical Treatments?**

In the past 30 years, major strides have been made in the treatment of osteoporosis. Evidence-based reports systematically reviewing the data from randomized clinical trials, including meta-analyses for each of the major treatments, are available and permit conclusions regarding the role of each modality of osteoporosis therapy.

Calcium and vitamin D intake modulates age-related increases in parathyroid hormone (PTH) levels and bone resorption. Randomized clinical trials have demonstrated that adequate calcium intake from diet or supplements increase spine BMD and reduce vertebral and nonvertebral fractures. Low levels of 25-OH vitamin D are common in the aging population, and significant reductions in hip and other nonvertebral fractures have been observed in patients receiving calcium and vitamin D3 in prospective trials. The maximal effective dose of vitamin D is uncertain, but thought to be 400 to 1,000 IU/day. There is consensus that adequate vitamin D and calcium intakes are required for bone health. The therapeutic effects of most of the clinical trials of various drug therapies for osteoporosis have been achieved in the presence of calcium and vitamin D supplementation among control and intervention groups. Optimal treatment of osteoporosis with any drug therapy also requires calcium and vitamin D intake meeting recommended levels. The preferred source of calcium is dietary. Calcium supplements need to be absorbable and should have USP designation.

Physical activity is necessary for bone acquisition and maintenance through adulthood. Complete bed rest and microgravity have devastating effects on bone. Trials of exercise intervention show most of the effect during skeletal growth and in very inactive adults. Effects beyond those directly on bone, such as improved muscular strength and balance, may be
very significant in fracture-risk reduction. Trials in older adults have successfully used various forms of exercise to reduce falls. High-impact exercise (weight training) stimulates accrual of bone mineral content in the skeleton. Lower impact exercises, such as walking, have beneficial effects on other aspects of health and function, although their effects on BMD have been minimal.

Randomized placebo-controlled trials (RCTs) of cyclic etidronate, alendronate, and risedronate analyzed by a systematic review and meta-analysis have revealed that all of these bisphosphonates increase BMD at the spine and hip in a dose-dependent manner. They consistently reduce the risk of vertebral fractures by 30 to 50 percent. Alendronate and risedronate reduce the risk of subsequent nonvertebral fractures in women with osteoporosis and adults with glucocorticoid-induced osteoporosis. There is uncertainty about the effect of anti-resorptive therapy in reducing nonvertebral fracture in women without osteoporosis. In RCTs, the relative risk of discontinuing medication due to an adverse event with each of the three bisphosphonates was not statistically significant. The safety and efficacy of this therapy in children and young adults has not been evaluated. Since subjects in clinical trials may not always be representative of the community-based population, an individual approach to treatment is warranted.

Hormone replacement therapy (HRT) is an established approach for osteoporosis treatment and prevention. Many short-term studies and some longer term studies with BMD as the primary outcome have shown significant efficacy. Observational studies have indicated a significant hip fracture reduction in cohorts of women who maintain HRT therapy; still there is a paucity of trials with fractures as the endpoint. HRT trials have shown decreased risk of vertebral fractures, but there have been no trials of estrogen with hip fracture as the primary outcome.

The development of selective estrogen receptor modulators (SERMs) has been an important new thrust in osteoporosis research. The goal of these agents is to maximize the beneficial effect of estrogen on bone and to minimize or antagonize
the deleterious effects on the breast and endometrium. Raloxifene, a SERM approved by the FDA for the treatment and prevention of osteoporosis, has been shown to reduce the risks of vertebral fracture by 36 percent in large clinical trials. Tamoxifen, used in the treatment and prevention of breast cancer, can maintain bone mass in postmenopausal women. However, effects on fracture are unclear.

There is a great deal of public interest in natural estrogens, particularly plant-derived phytoestrogens. These compounds have weak estrogen-like effects, and although some animal studies are promising, no effects on fracture reduction in humans have been shown. Salmon calcitonin has demonstrated positive effects on BMD at the lumbar spine, but this effect is less clear at the hip. Other than a recently completed randomized controlled trial of nasal calcitonin, no analysis of fracture risk is available. The PROOF study revealed a significant reduction in vertebral fracture risk at the 200 IU dose but not at the 100 IU or 400 IU dose. The absence of dose response, a 60 percent dropout rate, and the lack of strong supporting data from BMD and markers decrease confidence in the fracture risk data from this trial. Nonpharmacologic interventions directed at preventing falls and reducing their effect on fractures have been promising. These include studies to improve strength and balance in the elderly, as well as using hip protectors to absorb or deflect the impact of a fall.

Multifactorial approaches to preventing falls, as well as improving bone mass through combinations of interventions, suggest promising new directions.

**Should the Response to Treatment Be Monitored?**

Several approaches have been introduced for the monitoring of patients receiving therapies for osteoporosis. The goals of monitoring are to increase adherence to treatment regimens and determine treatment responses. Many individuals do not continue prescribed therapy or do not adhere to a treatment protocol, even when enrolled in formal clinical trials. Monitoring by densitometry or measurements of bone markers have
not been shown to be effective in improving compliance, and more research is needed about how to improve adherence to treatment protocols.

The best tests for monitoring treatment response would reflect the largest changes with the least error, and these assessment tools are not readily available. The Fracture Intervention Trial (FIT) reveals an additional problem with monitoring, the statistical phenomenon of regression to the mean. In this study, the larger the bone loss in the first year, the greater the gain the next year, for both the placebo and active treatment groups. Therefore, physicians should not stop or change therapies with demonstrated efficacy solely because of modest loss of bone density or adverse trends in markers of bone turnover.

Orthopaedic Management of Osteoporotic Fractures

While proximal femur (hip) fractures comprise nearly 20 percent of all osteoporotic fractures, this injury is among the most devastating of all the osteoporotic fractures and is responsible for the greatest expenditure of health care resources. The 1-year mortality rate following hip fracture is about 1 in 5. As many as two-thirds of hip fracture patients never regain their preoperative activity status. Early surgical management of hip fractures is associated with improved outcomes and decreased perioperative morbidity.

The adverse health, functional and quality of life effects of vertebral (spine) fractures are commonly underestimated, and such fractures are associated with increased mortality. The occurrence of a single vertebral fracture substantially increases the likelihood of future fractures and progressive kyphotic deformity. Due to the challenges of reconstruction of osteoporotic bone, open surgical management is reserved only for those rare cases that involve neurologic deficits or an unstable spine. Recently, there has been a burgeoning interest in two “minimally invasive” procedures for management of acute vertebral fractures, vertebroplasty and kyphoplasty, which involve the injection of polymethylmethacrylate bone cement into the fractured vertebra. Anecdotal reports with
both techniques claim frequent acute pain relief; however, neither technique has been subjected to a controlled trial to demonstrate the benefits over traditional medical management. Furthermore, the long-term effect of one or more reinforced rigid vertebrae on the risk of fracture of adjacent vertebrae is unknown for both of these procedures.

Several issues are critically important to the orthopaedic management of acute osteoporotic fractures. It is most important to avoid the misconception that the only treatment required of an osteoporotic fracture is management of the acute fracture itself. Management during the peri-fracture period must consider blood clot prevention (mechanical or pharmacologic) in patients who will have delayed ambulation, the avoidance of substances that may inhibit fracture repair (nicotine, corticosteroids), and the frequent need for supplemental caloric intake. Finally, since less than 5 percent of patients with osteoporotic fractures are referred for medical evaluation and treatment, more aggressive diagnostic and therapeutic intervention of this population represents an opportunity to prevent subsequent fractures. Physicians treating the acute fracture should initiate an outpatient evaluation of the patient for osteoporosis and a treatment program, if indicated, or refer the patient for an osteoporosis assessment.
What Are the Directions for Future Research?

The following questions, issues, and concerns should be addressed:

• Peak bone mass is an important factor in determining long-term fracture risk. Strategies to maximize peak bone mass in girls and boys are essential, including how to identify and intervene in disorders that can impede the achievement of peak bone mass in ethnically diverse populations, and, to determine how long these interventions should last. More research regarding the risks for fracture in chronic diseases affecting children is needed. What is the impact of calcium deficiency and vitamin D deficiency in childhood, and can it be reversed? How does gonadal steroid insufficiency, pubertal delay, or undernourishment impact bone mass? What is known about the use of bisphosphonates or other agents in the treatment of children with osteoporosis?

• Genetic factors leading to osteoporosis are being identified. These factors may relate to bone mass acquisition, bone remodeling, or bone structure. Pharmacogenetic approaches for identifying and targeting specific genetic factors predisposing to osteoporosis need to be developed.

• Glucocorticoid use is a common cause of secondary osteoporosis and associated fractures. What is the impact of glucocorticoid-induced osteoporosis in adults and children? What are the mechanisms of disease? What novel approaches can be taken to stimulate bone formation in this condition? Development of glucocorticoids that avoid effects on the skeleton are needed.

• Secondary causes of osteoporosis are prevalent. A number of risk factors have been identified, including specific disease states and medication use. How should patients be identified for diagnosis and treatment of osteoporosis? What is known about the use of bisphosphonates or other agents in young adults with secondary osteoporosis?
What is known about the causes of osteoporosis in peri-menopausal women? How should they be monitored for treatment response? Are therapies for improving bone mass in postmenopausal women effective in secondary causes?

- There is a need for prospective studies of gender, age, and ethnically diverse individuals to provide data that will permit more accurate fracture risk identification in these populations. Fracture risk is a combination of bone-dependent and bone-independent factors. Bone-independent factors include muscle function and cognition, which also contribute to falls leading to fractures. A comprehensive assessment of bone-dependent and bone-independent factors should be included. There is a need for a comprehensive assessment of a validated risk assessment tool. What is the best way to identify patients in need of treatment for osteoporosis? An algorithm should be constructed that incorporates risk factors for fracture in addition to assessment of bone density. What is the best use of surrogate markers of bone turnover to determine osteoporosis, and how does this impact on fracture risks?

- Quality of life is significantly impaired by osteoporosis. Future research should characterize and validate quality-of-life tools in patients across gender, age, and race or ethnicity. It will be important to identify effects of fracture risk and intervention on quality of life. Quality of life should be incorporated as an outcome in clinical trials evaluating fracture risk and therapy. In addition, the psychosocial and financial effects of osteoporosis on caregivers and family dynamics should be considered.

- There are no available data to suggest which asymptomatic patients should have screening bone-density tests done or when screening is justified. Information regarding screening guidelines is important to obtain.

- Neuropsychiatric disorders may cause or be the result of osteoporosis. Specific psychiatric disorders, including depression and anorexia nervosa, are associated with osteoporosis or clinical fractures. Medications used to treat psychiatric or neurologic disorders may cause
osteoporosis, and the diagnosis of osteoporosis may have psychological implications. Research efforts into the relationship between neuropsychiatric disorders and fracture risk should be strongly encouraged.

- There is an urgent need for randomized clinical trials of combination therapy, which includes pharmacologic, dietary supplement, and lifestyle interventions (including muscle strengthening, balance, and management of multiple drug use, smoking cessation, psychological counseling, and dietary interventions). Primary outcomes would be fractures, and secondary outcomes would include quality of life and functional capability. Cost-effectiveness evaluation should be considered in such a trial.

- What is the optimal evaluation and management of fractures? What diagnostic and management paradigm should be employed? What are the long-term consequences of osteoporosis and clinical fractures on nonskeletal body systems? What measures can be taken to prevent subsequent fractures?

- Anabolic agents that stimulate bone formation, such as PTH and fluoride, have been evaluated. Meta-analysis of fluoride therapy revealed no protective effects on fracture risk. PTH peptides are the most promising but are still in clinical trials. Other factors, including growth hormones, are under investigation. There is a critical need to develop and assess anabolic agents that stimulate bone formation.

- Assure accessibility to treatment for people regardless of income and geography.

- There is a need to determine the most effective method of educating the public and health care professionals about the prevention, diagnosis and treatment of osteoporosis.

- There is a need to improve the reporting of BMD and fracture risk so it is understandable to medical specialists and can be explained to patients.
• Study is needed to determine the efficacy and safety of long-term administration of various drug interventions in maintaining BMD and preventing fractures.

• Trials of dietary supplements are needed.

• Study is needed to understand the influence of nutrition on micronutrients and non-patentable medical interventions.

• Study is needed to understand cost-effectiveness and effectiveness of programs encouraging bone health.

• Study of interventions examining the long-term effects of fractures on health, function and quality of life is needed.
Conclusions

• Osteoporosis occurs in all populations and at all ages. Though more prevalent in white postmenopausal females, it often goes unrecognized in other populations.

• Osteoporosis is a devastating disorder with significant physical, psychosocial, and financial consequences.

• The risks for osteoporosis, as reflected by low bone density, and the risks for fracture overlap but are not identical.

• More attention should be paid to skeletal health in persons with conditions known to be associated with secondary osteoporosis.

• Clinical risk factors have an important, but as yet poorly validated, role in determining who should have BMD measurement, in assessing risk of fracture, and in determining who should be treated.

• Adequate calcium and vitamin D intake are crucial to develop optimal peak bone mass and to preserve bone mass throughout life. Supplementation of these two components in bioavailable forms may be necessary in individuals who do not achieve recommended intake from dietary sources.

• Gonadal steroids are important determinants of peak and lifetime bone mass in men, women, and children.

• Regular exercise, especially resistance and high-impact activities, contributes to development of high peak bone mass and may reduce the risk of falls in older individuals.

• Assessment of bone mass, identification of fracture risk, and determination of who should be treated are the optimal goals when evaluating patients for osteoporosis.

• Fracture prevention is the primary goal in the treatment of patients with osteoporosis.

• Several treatments have been shown to reduce the risk of osteoporotic fractures. These include therapies that enhance bone mass and reduce risk or consequences of falls.

• Adults with vertebral, rib, hip, or distal forearm fractures should be evaluated for the presence of osteoporosis and given appropriate therapy.
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Bibliography

The speakers listed above identified the following key references in developing their presentations for the consensus conference. A more complete bibliography prepared by the National Library of Medicine at the NIH, along with the references below, was provided to the technology assessment panel for their consideration. The full bibliography is available at the following Web site: http://www.nlm.nih.gov/pubs/cbm/osteoporosis.html

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