

PHYSICIAN'S GUIDE TO PREVENTION AND TREATMENT OF OSTEOPOROSIS

**Developed by the National Osteoporosis Foundation in
collaboration with**

*American Academy of Orthopaedic Surgeons
American Academy of Physical Medicine and Rehabilitation
American College of Obstetricians and Gynecologists
American College of Radiology
American College of Rheumatology
American Geriatrics Society
American Medical Association
International Society for Physical Medicine and Rehabilitation
The Endocrine Society*

Dedication

*This guide is dedicated to the memory of
Charles W. Slemenda, DrPH
September 24, 1950 - July 17, 1997*



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ATTENTION PHYSICIANS

It is important to note that the recommendations developed in this report are intended to serve as a reference point for clinical decision making with individual patients. They are not intended to be rigid standards, limits, or rules. They can be tailored to individual cases to incorporate personal facts that are beyond the scope of this guide. Because these are recommendations and not rigid standards, they should not be interpreted as quality standards. Nor should they be used to limit coverage for treatments.

This guide was developed by an expert committee of the National Osteoporosis Foundation (NOF) in collaboration with a multispecialty council of medical experts in the field of bone health convened by the NOF. Some of the members of the Guidelines Committee have relationships with pharmaceutical companies, including serving on Scientific Advisory Boards, receiving speakers' fees, and research support. No member of the Development Committee has a significant financial relationship with any individual pharmaceutical company.

Readers are urged to consult current prescribing information on any drug, device, or procedure discussed in this publication.

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NOTE TO READERS

This updated guide is designed to serve as a basic reference on the prevention, diagnosis, and treatment of osteoporosis. Like the original 1999 Physician's Guide, it is based largely on an analysis of the evidence for prevention, diagnosis, and treatment of osteoporosis by the National Osteoporosis Foundation (NOF) in collaboration with a broad, multidisciplinary coalition of clinical experts. The purpose of the update is to keep the Physician's Guide current with new treatments and to stimulate more extensive and appropriate testing and treatment of those at risk of fractures. The NOF believes that there is insufficient evidence at this time to warrant changing the bone mineral density (BMD) based treatment thresholds; however, we anticipate that as research on the determinants of bone strength proceeds, the approach to identifying individuals at greatest risk for fracture (and thus in greatest need of treatment) will change in the next few years. Meanwhile, this guide is intended for use by physicians as a tool for clinical decision making in the treatment of individual patients.

The information in this guide is based mainly on evidence from randomized, controlled clinical trials. Data were gathered from published studies and evaluated by an expert panel assembled by the NOF. Thus, the guide primarily addresses postmenopausal white women. It does not address men, premenopausal women, or women of other races, since there are insufficient data available to formulate comparable recommendations for these populations. This does not imply that osteoporosis affects only postmenopausal white women. Until we have enough data to make specific recommendations for other populations, the risk factors currently identified for white women should be used for others on an individual basis to determine the need for bone density testing and treatment. Neither does the guide address secondary causes of osteoporosis, which should be excluded by clinical evaluation. Furthermore, all people should follow the universal recommendations for prevention in this guide.

The recommendations herein reflect an awareness of the cost and effectiveness of both diagnostic and treatment modalities. Some effective therapeutic options that would be prohibitively expensive on a population basis might remain a valid choice in individual cases under certain circumstances. This guide cannot and should not be used to govern health policy decisions about reimbursement or availability of services. Its recommendations are not intended as rigid standards of practice, but must be tailored for use by physicians in consultation with their patients.

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OSTEOPOROSIS: IMPACT AND OVERVIEW

EXECUTIVE SUMMARY

Osteoporosis is a silent disease until it is complicated by fragility fractures - fractures that can occur in the absence of trauma or following minimal trauma. These fractures are common and place an enormous medical and personal toll on aging individuals and a major economic toll on the nation. Osteoporosis can be prevented and can be diagnosed and treated before any fracture occurs. Importantly, even after the first fracture has occurred there are effective treatments to decrease the risk of further fracture. Prevention, detection, and treatment of osteoporosis should be a mandate of primary care physicians. This updated guide offers concise recommendations regarding prevention, risk assessment, diagnosis and treatment of postmenopausal osteoporosis. It includes indications for bone densitometry for intervention with pharmacologic agents. Since the NOF first published the guide in 1999, it has become increasingly clear that many patients are not being given appropriate information about prevention, many patients are not having appropriate testing to diagnose osteoporosis or establish osteoporosis risk, and once diagnosed (by testing or by the occurrence of a fracture) too many patients are not being prescribed any of the FDA approved, effective therapies.

SYNOPSIS OF MAJOR RECOMMENDATIONS TO THE PHYSICIAN

-  Counsel all women on the risk of osteoporosis and related fractures.
-  Advise all patients to consume adequate amounts of calcium (at least 1200 mg/d, including supplements if necessary) and vitamin D (400 to 800 IU per day for individuals at risk of deficiency).
-  Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures.
-  Advise patients to avoid tobacco smoking and excessive alcohol intake.
-  Recommend BMD testing to all women aged 65 and older.
-  Recommend BMD testing to younger postmenopausal women who have one or more risk factors (other than being white, postmenopausal and female).
-  Recommend BMD testing to postmenopausal women who have suffered a fragility fracture to confirm the diagnosis and determine disease severity.
-  Initiate therapy to reduce fracture risk in postmenopausal women with BMD T-scores by central dual x-ray absorptiometry (DXA) below -2 in the absence of risk factors and in women with T-scores below -1.5 if one or more risk factors is present.
-  Consider postmenopausal women with vertebral or hip fractures candidates for osteoporosis treatment.
-  Current pharmacologic options for osteoporosis prevention and/or treatment are bisphosphonates (alendronate and risedronate), calcitonin, estrogens and/or hormone therapy, parathyroid hormone (PTH 1-34) and raloxifene.

SCOPE OF THE PROBLEM

Osteoporosis is the most common bone disease in humans. It is characterized by low bone mass, microarchitectural deterioration, compromised bone strength, and an increase in the risk of fracture. Osteoporosis is often defined clinically by an intermediate outcome, low BMD. Osteoporosis is a risk factor for fracture just as hypertension is for stroke.

Osteoporosis affects an enormous number of people, and its prevalence will increase as the population ages. Based on data from the National Health and Nutrition Examination Survey III and from the 2000 National Census, the NOF has estimated that in 2002, 20% of postmenopausal white women in the United States have osteoporosis, and an additional 52% have low bone density at the hip. In the whole population, more than 7.8 million have osteoporosis and an additional 21.8 million women have low bone density of the hip. One out of every two white women will experience an osteoporotic fracture at some point in her lifetime.

MEDICAL IMPACT

Fractures and their complications are the relevant clinical sequelae of osteoporosis. The most common fractures are those of the vertebrae (spine), proximal femur (hip), and distal forearm (wrist). However, almost all fractures in older adults are due in part to low bone mass

Fractures may be followed by full recovery or by chronic pain, disability, and death. Hip fractures result in 10% to 20% excess mortality within 1 year; additionally, one-third of patients with a hip fracture will fracture the opposite hip. Up to 25% of hip fracture patients may require long-term nursing home care, and only 40% fully regain their prefracture level of independence.

Vertebral fractures also cause significant complications including back pain, height loss, kyphosis, and death. Postural and height changes associated with kyphosis may limit activity, including bending and reaching. Multiple thoracic fractures may result in restrictive lung disease, and lumbar fractures may alter abdominal anatomy, leading to constipation, abdominal pain, distention, reduced appetite, and premature satiety.

Hip and vertebral fractures can also cause psychological symptoms, most notably depression and loss of self-esteem, as patients grapple with pain, physical limitation, and lifestyle and cosmetic changes. Anxiety, fear, and anger may also impede recovery. The high morbidity and consequent dependency associated with these fractures strain interpersonal relationships and social roles for patients and their families.

ECONOMIC TOLL

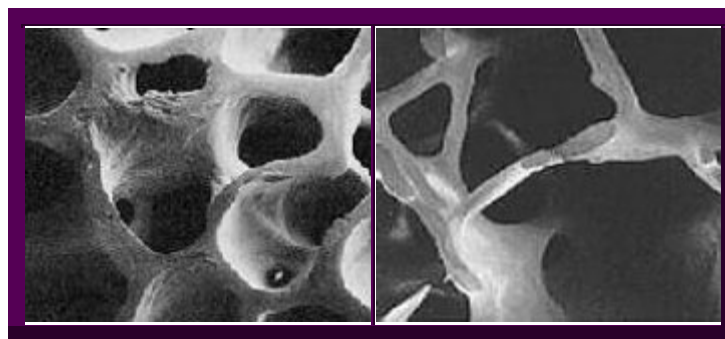
Osteoporotic fractures create a heavy economic burden. In 1995, they were the presumed cause of 432,000 hospital admissions, almost 2.5 million physician visits, and about 180,000 nursing home admissions in the United States. The annual cost to the health care system associated with osteoporotic fractures has been estimated at \$17 billion (2001 dollars), with a single hip fracture costing an estimated \$40,000 (in 2001 dollars). By one estimate, the number of hip fractures and their associated costs could more than triple by the year 2040.

BASIC PATHOPHYSIOLOGY

Bone mass in adults equals peak bone mass (achieved by age 25-30 years) minus the amount of bone subsequently lost. Peak bone mass is determined largely by genetic factors, with contributions from nutrition, endocrine status, physical activity, and health during growth. The process of bone remodeling that maintains a healthy skeleton is a kind of preventive maintenance program, continually removing older bone and replacing it with new bone. Bone loss occurs when the balance between bone removal and replacement is altered, resulting in greater bone removal than replacement. This imbalance occurs with menopause and advancing age. At menopause, the rate of bone remodeling increases, magnifying the impact of the remodeling imbalance. The consequence is reduced bone mass, disordered skeletal architecture, and an increase in fracture risk.

Figure 1 shows the changes within cancellous bone as a consequence of bone loss. Individual trabecular plates of bone are lost, leaving an architecturally weakened structure with significantly reduced mass. Increasing evidence suggests that rapid rates of bone remodeling (as measured by markers of bone resorption or formation) increases bone fragility and fracture risk.

**FIGURE 1. MICROGRAPHS
NORMAL VS. OSTEOPOROTIC BONE**

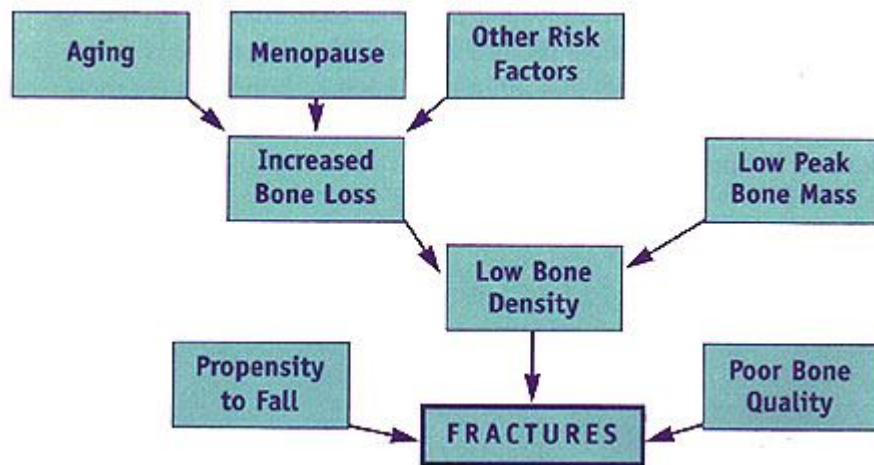


Normal

Osteoporotic

Bone loss leads to an increased risk of fracture that is magnified by other aging-associated changes. **Figure 2** shows the factors associated with an increased risk of osteoporotic fractures.

FIGURE 2. PATHOGENESIS OF OSTEOPOROTIC FRACTURES



Modified with permission from Riggs BL, Melton LJ, eds. *Osteoporosis: Etiology, Diagnosis, and Management*. Raven Press. New York. 1988. 162. Used by permission of Lippincott Williams-Wilkins.

RISK ASSESSMENT

After menopause, all women should be evaluated clinically for osteoporosis risk in order to determine the need for BMD testing. In general, the more risk factors a woman has, the greater her risk of fracture.

Osteoporosis is preventable and treatable, but because there are no warning signs until a fracture occurs, many people are not being diagnosed in time to receive effective therapy during the early phase of the disease. The major factors associated with an increased risk of osteoporotic fracture in postmenopausal women are shown in Table 1. Osteoporosis can also result from several medical conditions (see Table 2a) and from use of several medications (see Table 2b).

TABLE 1.

MAJOR RISK FACTORS FOR OSTEOPOROSIS AND RELATED FRACTURES IN CAUCASIAN POSTMENOPAUSAL WOMEN:

- Personal history of fracture as an adult
- History of fragility fracture in a first-degree relative
- Low body weight (< about 127 lbs)
- Current smoking
- Use of oral corticosteroid therapy for more than 3 months

ADDITIONAL RISK FACTORS

- Impaired vision
- Estrogen deficiency at an early age (<45 yrs)
- Dementia
- Poor health/frailty
- Recent falls
- Low calcium intake (lifelong)
- Low physical activity
- Alcohol in amounts >2 drinks per day

DIAGNOSIS

Consider the possibility of osteoporosis and fracture risk in all postmenopausal women, based on the presence of the risk factors and conditions outlined in Tables 1 and 2. The diagnosis can be established in patients who have never sustained a fragility fracture by measurement of BMD.

Metabolic bone diseases other than osteoporosis, such as hyperparathyroidism or osteomalacia, may be associated with a low BMD. Many of these diseases have very specific therapies and it is appropriate to complete a history and physical examination before attaching a diagnosis of osteoporosis on the basis of a low BMD alone. In patients in whom a specific secondary, treatable cause of osteoporosis is being considered (see Table 2a), relevant blood and urine studies (such as urine calcium, thyrotropin, protein electrophoresis, cortisol or antibodies associated with gluten-sensitive enteropathy) should be obtained prior to initiating therapy. For instance, elderly patients with recent fractures should be evaluated for osteomalacia with a 25-hydroxyvitamin D level. Limited biochemical testing (such as serum calcium, creatinine, etc.) may be appropriate for anyone with osteoporosis.

TABLE 2A. MEDICAL CONDITIONS THAT MAY BE ASSOCIATED WITH AN INCREASED RISK OF OSTEOPOROSIS

AIDS/HIV	Inflammatory Bowel Disease
Amyloidosis	Insulin-dependent diabetes mellitus
Ankylosing spondylitis	Lymphoma and leukemia
Chronic obstructive pulmonary disease	Malabsorption syndromes
Congenital porphyria	Mastocytosis
Cushing's syndrome	Multiple myeloma
Eating disorders (e.g., anorexia nervosa)	Multiple sclerosis
Female athlete triad	Pernicious anemia
Gastrectomy	Rheumatoid arthritis
Gaucher's Disease	Severe liver disease, especially primary biliary cirrhosis
Hemochromatosis	Spinal cord transection
Hemophilia	Sprue
Hyperparathyroidism	Stroke (CVA)
Hypogonadism, primary and secondary (e.g., amenorrhea)	Thalassemia
Hypophosphatasia	Thyrotoxicosis
Idiopathic scoliosis	Tumor secretion of parathyroid hormone-related peptide
Inadequate diet	Weight loss

TABLE 2B. DRUGS THAT MAY BE ASSOCIATED WITH REDUCED BONE MASS IN ADULTS

Aluminum	Lithium
Anticonvulsants (phenobarbital, phenytoin)	Long-term heparin use
Cytotoxic drugs	Progesterone, parenteral, long-acting
Glucocorticosteroids and adrenocorticotropin	Supraphysiologic thyroxine doses
Gonadotropin-releasing hormone agonists	Tamoxifen (premenopausal use)
Immunosuppressants	Total parenteral nutrition

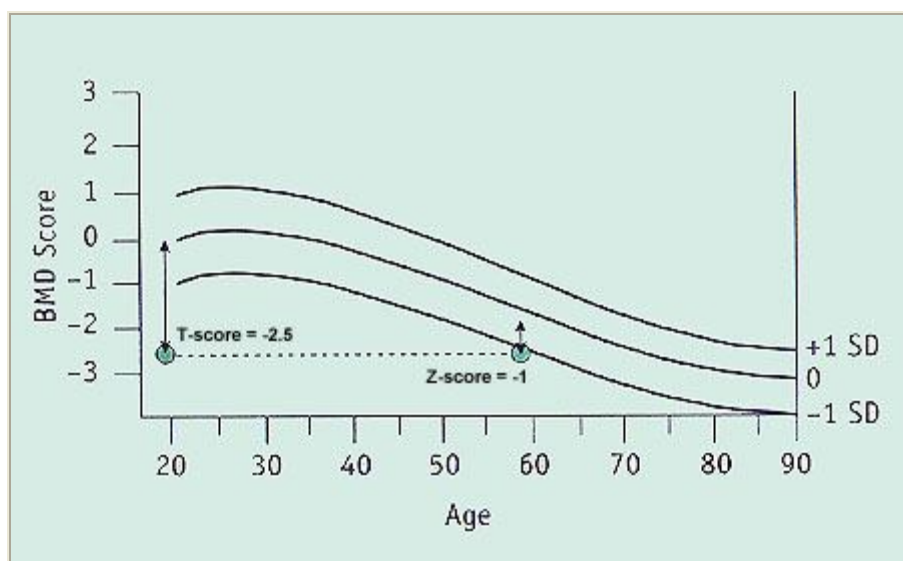
BMD MEASUREMENT

BMD measurement can be used to establish or confirm a diagnosis of osteoporosis and predict future fracture risk. BMD has a continuous, graded, inverse relationship to the risk of fracture: the lower the BMD, the greater the fracture risk. Many individuals have slight builds, and their BMD will generally be lower.

Measurements of BMD at any skeletal site have value in predicting fracture risk. A variety of densitometers are in clinical use and provide reliable assessment of fracture risk. However, hip BMD is the best predictor of hip fractures, and it predicts fractures at other skeletal sites. Thus, the recommendations made here are based on measurements of the hip.

BMD is expressed as a relationship to two norms: the expected BMD for the patient's age and sex (Z-score), or for "young normal" adults of the same sex (T-score). The difference between the patient's score and the norm is expressed in standard deviations (SD) above or below the mean. (Usually, 1 SD equals 10 to 20% of the bone density value.) T-scores decline in parallel with the steady drop in bone mass that occurs with aging (see Figure 3). This guide uses central DXA T-scores for clinical decision making.

FIGURE 3. Z- AND T-SCORES



In the above example, the BMD of a 57-year-old woman is expressed in comparison to young-normal average BMD (T-score) and age-matched average BMD (Z-score). Thus, this same woman has a Z-score of -1 and a T-score of -2.5.

Defining Osteoporosis by BMD

The World Health Organization has established the following definitions based on bone mass measurement at the spine, hip, or wrist in white postmenopausal women:

Normal: BMD is within 1 SD of a “young normal” adult (T-score at -1.0 and above)

Low bone mass (osteopenia): BMD is between 1 and 2.5 SD below that of a “young normal” adult (T-score between -1 and -2.5)

Osteoporosis: BMD is 2.5 SD or more below that of a “young normal” adult (T-score at or below -2.5). Women in this group who have already experienced one or more fractures are deemed to have severe or “established” osteoporosis.

Although these definitions are necessary to establish the prevalence of osteoporosis, they should not be used as the sole determinant of treatment decisions.

WHO SHOULD BE TESTED?

The decision to test for BMD should be based on an individual's risk profile, and testing is never indicated unless the results could influence a treatment decision.

BMD testing should be performed on:

1. **All women aged 65 and older regardless of risk factors.***
2. **Younger postmenopausal women with one or more risk factors (other than being white, postmenopausal, and female).**
3. **Postmenopausal women who present with fractures (to confirm diagnosis and determine disease severity)**

** Footnote: Medicare covers BMD testing for the following individuals age 65 and older:*

- *Estrogen deficient women at clinical risk for osteoporosis*
- *Individuals with vertebral abnormalities*
- *Individuals receiving, or planning to receive, long-term glucocorticoid (steroid) therapy*
- *Individuals with primary hyperparathyroidism*
- *Individuals being monitored to assess the response or efficacy of an approved osteoporosis drug therapy*

Medicare permits individuals to repeat BMD testing every two years.

A suggested algorithm for the evaluation and management of osteoporotic fracture risk is shown in **Figure 4**.

FIGURE 4. EVALUATING FRACTURE RISK

BMD TESTING TECHNIQUES

All of the tests described below are good predictors of future fracture.

Dual x-ray absorptiometry (DXA). DXA can be used to measure BMD in the spine, hip, or wrist, the most common sites for osteoporotic fractures. A DXA measurement can be completed in a few minutes with radiation exposure that is approximately one tenth that of a standard chest x-ray. Hip BMD is the best predictor of hip fracture risk. Central DXA of the hip and/or spine is the preferred measurement for definitive diagnosis.

Peripheral dual x-ray absorptiometry (pDXA) and single-energy x-ray absorptiometry (SXA). These techniques measure bone density in the forearm, finger, and sometimes the heel.

Quantitative computed tomography (QCT). QCT measures trabecular and cortical bone density at several skeletal sites, but is most commonly used to measure trabecular bone density in the spine. It is also possible to measure trabecular and cortical bone density in the periphery by pQCT (peripheral QCT).

Ultrasound densitometry. Ultrasound assesses bone in the heel, tibia, patella, or other peripheral sites where the bones are relatively superficial. Ultrasound measurements are generally not as precise as DXA or SXA, but appear to predict fracture risk as well as other measures of bone density.

BIOCHEMICAL MARKERS

Markers of bone turnover in the serum or urine are sometimes used to help assess risk of fracture, predict bone loss, or assess response to antiresorptive therapy. However, biochemical marker tests cannot replace BMD testing.

UNIVERSAL RECOMMENDATIONS FOR ALL PATIENTS

Several interventions to reduce fracture risk can be recommended to the general population. These include an adequate intake of calcium and vitamin D, lifelong participation in regular weight-bearing and muscle-strengthening exercise, avoidance of tobacco use, identification and treatment of alcoholism, and treatment of other risk factors for fracture such as impaired vision.

ADEQUATE INTAKE OF CALCIUM AND VITAMIN D

Advise all individuals to obtain an adequate intake of dietary calcium (at least 1200 mg per day, including supplements if necessary) and vitamin D (400 to 800 IU per day for individuals at risk of deficiency).

An adequate intake of calcium lifelong is necessary for the acquisition of peak bone mass and maintenance of bone health. The skeleton contains 99% of the body's calcium stores; when the exogenous supply is inadequate, bone tissue is resorbed from the skeleton to maintain serum calcium at a constant level.

Controlled clinical trials have demonstrated that the combination of supplemental calcium and vitamin D can reduce the risk of fracture. Providing adequate daily calcium and vitamin D is a safe and inexpensive way to help reduce fracture risk. The NOF supports the National Academy of Sciences (NAS) recommendation that women over age 50 consume at least 1200 mg per day of elemental calcium. The safe upper limit for total calcium intake has been set at 2500 mg/day.

TABLE 3. ESTIMATING DAILY DIETARY CALCIUM INTAKE

STEP 1: Estimate calcium intake from calcium rich foods*					
Product	No. of Servings/Day	Calcium Content per Serving, mg			Calcium, mg
Milk (8 oz)	_____	X	300	=	_____
Yogurt (8 oz)	_____	X	400	=	_____
Cheese (1 oz)	_____	X	200	=	_____
Fortified Foods or Juices	_____	X	80-1000**	=	_____
STEP 2: Total from above + 250 mg for nondairy sources = total dietary calcium					
* About 75% to 80% of the calcium consumed in American diets is from dairy products.					
**Calcium content of fortified foods varies.					

Table 3 illustrates a simple method for estimating the calcium content of a patient's diet. Increasing dietary calcium is the first-line approach, but calcium supplements should be used when an adequate dietary intake cannot be achieved. Postmenopausal American women typically consume about 600 mg

per day of calcium in their diets.

Vitamin D plays a major role in calcium absorption and bone health. Chief dietary sources of vitamin D include vitamin-D-fortified milk (400 IU per quart) and cereals (40 to 50 IU per serving), egg yolks, salt-water fish, and liver. Some calcium supplements and most multivitamin tablets also contain vitamin D. An intake of 400 to 600 IU of vitamin D per day is recommended by the NAS for all adults over age 50. NOF recommends 800 IU per day for those at risk of deficiency, such as elderly, chronically ill, housebound, or institutionalized individuals. The safe upper limit for vitamin D intake set by the NAS is 2000 IU per day.

REGULAR WEIGHT-BEARING EXERCISE

Recommend regular weight-bearing and muscle-strengthening exercise to reduce the risk of falls and fractures.

Among its many health benefits, weight-bearing and muscle-strengthening exercise can improve agility, strength, and balance, which may reduce the risk of falls. In addition, exercise may increase bone density modestly. The NOF strongly endorses lifelong physical activity at all ages, both for osteoporosis prevention and overall health, as benefits are lost when the person stops exercising. Weight-bearing exercise (in which bones and muscles work against gravity as the feet and legs bear the body's weight) includes walking, jogging, Tai-Chi, stair climbing, dancing, and tennis. Muscle strengthening includes weight lifting and other resistive exercises. Before an individual with osteoporosis initiates a new vigorous exercise program, such as running or heavy weight lifting, a physician's evaluation is appropriate.

FALL PREVENTION

In addition to exercise as described above, strategies to reduce risk of falling include, but are not limited to, checking and correcting vision and hearing, evaluating any neurological problems, reviewing prescription medications for side effects that may affect balance and stability and providing a check list for improving safety at home. Wearing undergarments with hip protectors (brands: Safehip®, HIPS®, HipGuard®, ImpactWear®) may protect an individual from injuring the hip in the event of a fall. Hip protectors should be considered for patients who have significant risk factors for falling or for patients who have previously fractured a hip.

AVOIDANCE OF TOBACCO USE AND EXCESSIVE ALCOHOL INTAKE

Advise patients to avoid tobacco smoking. Recognize and treat patients with excessive alcohol intake.

The use of tobacco products is detrimental to the skeleton as well as to overall health. The NOF strongly encourages a smoking cessation program as an osteoporosis intervention.

Moderate alcohol intake has no known negative effect on bone and may even be associated with slightly higher bone density and lower risk of fracture in postmenopausal women. However, excessive alcohol intake is detrimental to bone health and requires treatment when identified.

PHARMACOLOGIC OPTIONS

All patients being considered for drug treatment of osteoporosis should also be counseled on risk factor reduction. Patients should be counseled specifically on the importance of calcium, vitamin D, and exercise as part of any treatment program for osteoporosis. Prior to initiating treatment, patients should be evaluated for secondary causes of osteoporosis and have central DXA measurements, when available. The percentage risk reductions for vertebral and non-vertebral fractures cited below are based on the Osteoporosis Research Advisory Group Meta-Analyses of Therapies for Postmenopausal Osteoporosis. Caution should be exercised when directly comparing risk reductions for the different drugs, as the patient populations studied were often dissimilar.

WHO SHOULD BE TREATED

Initiate therapy to reduce fracture risk in women with

- **BMD T-scores below -2.0 by central DXA with no risk factors**
- **BMD T-scores below -1.5 by central DXA with one or more risk factors**
- **A prior vertebral or hip fracture**

Since bone loss accelerates around the time of menopause, should therapy be initiated at this juncture to prevent bone loss, even in women with relatively normal bone density? The approach is reasonable in theory, but there are limited data about the effectiveness for fracture prevention and long-term safety for most of the approved therapies.

US FDA-APPROVED DRUGS FOR OSTEOPOROSIS

U.S. Food and Drug Administration-approved pharmacologic options for the prevention and/or treatment of postmenopausal osteoporosis include, in alphabetical order: bisphosphonates (alendronate, risedronate), calcitonin, estrogens (estrogen and/or hormone therapy), parathyroid hormone [PTH(1-34)], and selective estrogen receptor modulators or SERMs (raloxifene). Please see the Physicians Desk Reference for more detailed information about these drugs and for their other indications (e.g., bisphosphonate indications for male osteoporosis and for glucocorticoid-induced osteoporosis).

BISPHOSPHONATES

Alendronate

Brand name: Fosamax®

Alendronate is approved by the FDA for the prevention (5 mg daily and 35 mg weekly) and treatment (10 mg daily and 70 mg weekly) of osteoporosis in postmenopausal women. Controlled clinical trials indicate that over a 3 to 4 year period alendronate increases bone mass and reduces the incidence of vertebral, hip, and all non-vertebral fractures by 50%.*

Risedronate

Brand name: Actonel®

Risedronate (5 mg daily dose and 35 mg weekly) is approved by the FDA for the prevention and treatment of postmenopausal osteoporosis. Controlled clinical trials indicate that risedronate increases bone mass and reduces the risk of vertebral fractures by 40% and all non-vertebral fractures by 30% over a 3-year period.*

**Footnote: As indicated above, direct comparisons of risk reductions for these drugs should be avoided.*

SIDE EFFECTS AND ADMINISTRATION OF BISPHOSPHONATES

Clinical trials have found the incidence of side effects in patients taking alendronate and risedronate to be no different than the incidence in the placebo groups. However, clinical experience suggests that some patients may experience upper gastrointestinal disorders such as dysphagia, esophagitis, and esophageal or gastric ulcer.

Alendronate and risedronate must be taken after a prolonged fast with 8 ounces of water (no other liquid), at least 30 minutes before eating or drinking. Patients should remain upright (sitting or standing) during this interval as well.

Calcitonin

Brand name: Miacalcin®

Salmon calcitonin is FDA-approved for the treatment of osteoporosis in women who are at least 5 years postmenopausal. It is delivered as a single daily intranasal spray that provides 200 international units (IU) of the drug. Subcutaneous administration by injection also is available. Controlled clinical trials indicate that calcitonin decreases the vertebral fracture rate by 54%. In the single large trial, however, it lowered vertebral fracture risk by 21%. It did not alter the non-vertebral fracture rate in any of the studies. Calcitonin is generally safe and well tolerated, although some patients experience rhinitis and, rarely, epistaxis.

Estrogen/Hormone Therapy (ET/HT)

ET brand names: e.g. Climara®, Estrace®, Estraderm®, Estratab®, Ogen®, Ortho-Est®, Premarin®, Vivelle®

HT brand names: e.g. Activella™, Femhrt®, Premphase®, Prempro®

Estrogen/hormone replacement therapy (ET/HT) is approved by the FDA for the prevention of osteoporosis, relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause.

Women who have not had a hysterectomy require HT, which contains progestin to protect the uterine lining. The Woman's Health Initiative (WHI) found that 5 years of HT (Prempro®) reduced the risk of clinical vertebral fractures and hip fractures by 34%. However, the FDA recommends that when their use is considered solely for prevention of osteoporosis, approved non-estrogen treatments should first be carefully considered.

ET/HT should not be used for the prevention of cardiovascular disease. The WHI reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli and deep vein phlebitis during 5 years of treatment with Prempro®. Other doses and combinations of estrogen and progestins were not studied and, in the absence of comparable data, their risks should be assumed to be comparable. Because of the risks, ET/HT should be used in the lowest possible doses for the shortest duration to meet treatment goals.

Parathyroid hormone [PTH (1-34)]

Brand name: Forteo®

PTH (1-34) is approved by the FDA for the treatment of osteoporosis in postmenopausal women. PTH (1-34) is an anabolic (bone-building) agent when administered by daily subcutaneous injection. PTH (1-34) was recently shown to decrease the risk of vertebral fractures by 65% and non-vertebral fractures by 54% after an average of 18 months of therapy.

PTH (1-34) is well tolerated although some patients experience leg cramps and dizziness. Because PTH (1-34) caused an increase in the incidence of osteosarcoma in rats, patients with an increased risk of osteosarcoma (e.g., patients with Paget's disease of bone, prior radiation therapy of the skeleton, bone metastases, hypercalcemia, or a history of skeletal malignancy) should not receive PTH (1-34) therapy. The safety and efficacy of PTH (1-34) has not been demonstrated beyond 2 years of treatment.

Raloxifene

Brand name: Evista®

Raloxifene is approved by the FDA for both prevention and treatment of osteoporosis in postmenopausal women. Raloxifene increases vertebral bone mass modestly and reduces the risk of vertebral fracture by 40 %. Currently, there is no evidence that it significantly reduces risk of non-vertebral fractures.

Raloxifene increases the risk of deep vein thrombosis to a degree similar to that observed with estrogen. It also increases hot flashes (~6% over placebo).*

**Footnote: Raloxifene appears to decrease the risk of estrogen-dependent breast cancer. Its effect on coronary heart disease is under investigation.*

Combination therapy (usually a bisphosphonate with a non-bisphosphonate) can provide additional small increases in BMD when compared with monotherapy; however, the impact of combination therapy on fracture rates is unknown. The added cost and potential side effects should be weighed against potential gains.

NON-FDA-APPROVED DRUGS FOR OSTEOPOROSIS

The NOF does not advocate the use of drugs not approved by the U.S. FDA for prevention or treatment of osteoporosis. These drugs are listed for information only. These non-approved agents include:

Calcitriol. This synthetic vitamin D analogue, which promotes calcium absorption, has been approved by the FDA for managing hypocalcemia and metabolic bone disease in renal dialysis patients. It is also approved for use in hypoparathyroidism, both surgical and idiopathic, and pseudohypoparathyroidism. No reliable data demonstrate a reduction of risk for osteoporotic fracture.

Other bisphosphonates (etidronate, ibandronate, pamidronate, tiludronate, zoledronic acid). These agents vary chemically from alendronate and risedronate but are in the same drug class. At the time of publication, none is approved for prevention or treatment of osteoporosis. Most of these medications are currently approved for other conditions including Paget's disease, hypercalcemia of malignancy, and myositis ossificans. Ibandronate, a bisphosphonate that can be given either intravenously or orally, and zoledronic acid, given intravenously, are under evaluation as treatment for osteoporosis.

Sodium fluoride. Through a process that is still unclear, sodium fluoride stimulates the formation of new bone. The quality of bone mass thus developed is also uncertain, and the evidence that fluoride reduces fracture risk is conflicting and controversial.

Tibolone. Tibolone is a tissue-specific, estrogen-like agent that may prevent bone loss and reduce menopausal symptoms but it does not stimulate breast or uterine tissue. It is indicated in Europe for the treatment of vasomotor symptoms of menopause and for prevention of osteoporosis but it is not currently approved for use in the United States.

MONITORING TREATMENT

Osteoporosis needs lifelong management. It is important to ask patients about adherence and encourage continued and appropriate compliance with their therapies to reduce fracture risk.

Many physicians monitor changes in BD by central DXA every year or two during pharmacologic therapy for osteoporosis. It is important to note that drugs may decrease a patient's risk of fracture even when there is no apparent increase in BMD. As with most tests, BMD has some precision error. Therefore, changes of less than 2 to 4% in the vertebrae and 3 to 6% at the hip from test to test can be due to the precision error of the method. Repeat bone density measurements for monitoring disease progression in response to therapy should generally be performed after 1 or 2 years. Two years is consistent with guidelines developed by the Centers for Medicare & Medicaid Services (CMS). Biochemical markers of bone turnover can be used to monitor response to treatment. Current evidence suggests that both the decrease in turnover and the increase in BMD induced by antiresorptive therapies contribute to their antifracture efficacy. Biochemical markers show considerable variability within individuals such that fairly large changes are required to indicate a treatment effect; however, with antiresorptive therapy, the changes are often substantial. .

PHYSICAL MEDICINE AND REHABILITATION

Physical medicine and rehabilitation can reduce disability, improve physical function, and lower risk of subsequent falls in patients with osteoporosis.

Fracture of the hip, vertebrae and wrist are associated with significant impairments and disability. Evaluation by a physiatrist and comprehensive rehabilitation intervention are often essential to ensure maximum functional restoration. Components of such a program frequently include a goal oriented exercise regimen, appropriate diet, modalities for pain relief, psychosocial support, and various assistive devices.

The 2002 NOF Health Professional's Guide to Rehabilitation of Patients with Osteoporosis provides additional information on this topic.

CONCLUSIONS

This guide has focused on the prevention, diagnosis, and treatment of osteoporosis in postmenopausal white women using the most common existing diagnostic and treatment methods available. Much is known about osteoporosis in this population. However, many additional issues urgently need epidemiologic, clinical, and economic research. Pressing questions include:

- How can we better assess bone strength and thus improve identification of patients at high risk for fracture?
- How can children, adolescents, and young adults maximize peak bone mass?
- What are the precise components (intensity, duration, frequency, type of exercise) of an effective exercise program for osteoporosis prevention and treatment?
- What should be done to identify and modify risk factors for falling?
- How effective are different pharmacotherapeutic agents in preventing fractures in patients with moderately low bone mass?
- What therapies are effective in preventing and treating osteoporosis in men, premenopausal women, and nonwhite women?
- What therapies are most effective in patients with eating disorders?
- What approaches are most effective in treating osteoporosis in disabled populations?
- How long should anti-resorptive therapies be continued?
- Are combination therapies useful and if so which are the useful combinations and when should they be used?
- Can we identify agents that will significantly increase bone mass and return bone structure to normal?

The NOF is committed to continuing the effort to answer these and other questions related to this debilitating disease, with the goal of eliminating osteoporosis as a threat to the health of present and future generations.

Additional resources:

- [Order](#) NOF resources for health professionals on-line.
- Order multiple copies of the *Physician's Guide* [on-line](#).