CME ARTICLE

The Management of the Patient with Osteoporosis—A Modern Epidemic

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This activity is designed for primary care physicians and healthcare policy makers.

GOAL
To understand the current approaches to the diagnosis and management of osteoporosis.

OBJECTIVES
1. To gain knowledge of the newer definitions of osteoporosis based on World Health Organization standards and to differentiate osteoporosis from other causes of low bone mineral content.
2. To understand the present concepts of bone markers and how they are used in the diagnosis and management of osteoporosis.
3. To gain knowledge in appropriate drug treatment for the prevention and treatment of osteoporosis.
4. To understand the role of bone densitometry measurements in the diagnosis of osteoporosis.

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As our population ages, increasing the number of elderly at risk, osteoporosis has emerged as a major public health problem. The morbidity and disability in the aging attendant on this disorder have necessitated our developing new methods of identifying risk factors for this disorder and newer prevention and treatment strategies.

Osteoporosis is a disorder in which bone has insufficient strength to prevent fractures under normal everyday living conditions (ie, fractures occur in the absence of trauma). In this condition there is both a loss of mineral content and underlying bone support structure (matrix). Fractures of the wrist (Colles' fracture), of the spine (vertebral), and of the hip (femoral neck) are the major ones seen in this disorder. However, any fractures can occur with lower traumatic force than would be true for normal bone.[1]

Primary osteoporosis is the result of bone loss related to aging and, in women, the additional loss of bone mineral that occurs with estrogen deficiency (menopause). Secondary osteoporosis is the result of disease processes that affect bone, such as hyperparathyroidism or hyperthyroidism, or secondary to treatment with drugs that affect bone mineral metabolism, especially steroids, such as prednisone.

Prevalence

In the United States there are 250,000 hip fractures reported each year (based on US health statistics, 1992). Vertebral fractures, which only rarely require hospitalization, are not easily counted. Usually these fractures are identified because of height changes in an individual or because of incidental findings on a chest X ray or on an X ray of the spine taken to determine the cause of back pain. Their number is estimated at more than 500,000 per year. Colles' fractures are the third common fracture associated with osteoporosis and are estimated to have an occurrence of about 300,000 cases per year. Other fractures that are largely due to accidents will occur with less force in someone who has osteoporosis than in someone with normal bone strength.[2]

The overall cost of these fractures has been estimated at approximately $8-10 billion per year. For each hip fracture, there is an estimated in-hospital stay of 17-19 days (based on HCFA data, 1995). Since hospitalization for vertebral fractures is rarely required, their economic impact is not clear. These people often have difficulty performing tasks requiring bending or lifting such as household chores and shopping. Following hip fracture, approximately 50% of patients need assistance with daily living, often nursing home care, especially those over 80 years of age. Even in younger patients, over 30% require assistance with tasks of daily living. Of those who return to their own home, 40% will require home care assistance.[3]

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Another 20% of hip fracture patients die of complications within 12 months of their hip fracture. Thus, it is obvious that hip fractures are a major cause of morbidity, mortality, and significantly increased healthcare costs. With an increase in the at-risk population, ie, over 80 years old, hip fractures can be expected to double in the early part of the next century.

Making the Diagnosis

Traditionally, the diagnosis of osteoporosis required an X ray of the bones. If it showed low bone mass with a fracture, the patient had osteoporosis. However, fractures are the outcome of the disorder rather than an indicator of the disorder of which they are a complication.

The World Health Organization (WHO) has created a standard for the diagnosis based on bone density (BD). This, though ignoring bone architecture, is the method of choice for making a diagnosis of osteoporosis. Because of the difference in the absolute numbers for bone calcium content as measured by

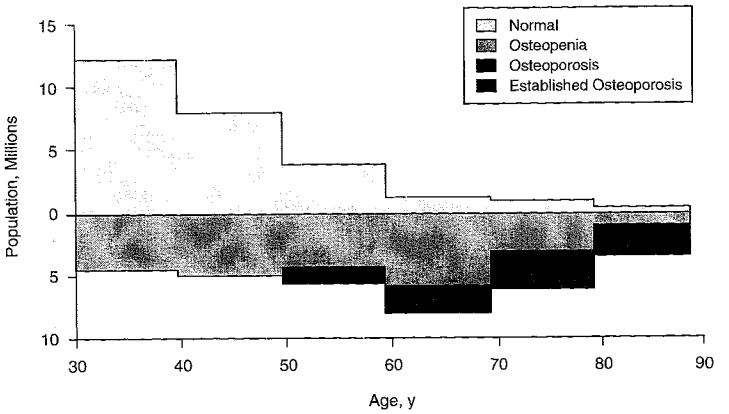

Figure 1. Estimated skeletal status of US white women in 1990, by age group. Osteopenia is bone density of the hip, spine, or distal forearm more than 1 but less than 2.5 SDs below the young normal mean (ages 25-40 years). Osteoporosis is bone density at 1 or more of these sites more than 2.5 SDs below the young adult mean (ages 25-40 years) and, when linked with a history of fracture, is deemed established osteoporosis. Numbers above the middle (horizontal) line represent the number of women with normal bone mineral density for each age group. Numbers below the middle line represent the numbers of women in the 3 categories of osteopenia and osteoporosis in proportion to the corresponding shaded regions.
Taken from Osteoporosis by P.D. Ross in *Arch Intern Med* 1996;156:1400. Copyright 1996. American Medical Association.

Table 1. Methods for Measuring Bone Density

1. X ray of Hand
■ Measure density of resultant X ray film of phalanges
■ Widely available with standard X ray equipment; varies with subject use of hands at work.
2. Dual Photon Absorptiometry
■ Specialized equipment requiring change of ionizing radiation source every 6 months, resulting in large variation in repetitive measurements over time.
■ Useful for spine, arm, or femoral neck.
3. Quantitative CT
■ Can use conventional CT scanner but requires specialized software and special standard preparation.
■ High-dose radiation to region of study (300 mrem).
■ Very good for measurement of vertebral bone density in subjects who already have osteoporotic changes or bony deformities
■ Can separate cancellous bone from cortical bone.
4. Dual Energy X ray (DEXA)
■ Presently the most accurate method for measuring bone density of the spine, arm, and femoral neck
■ Very low dose of radiation (1.5-2.0 mrem/procedure)
■ Calcium content values vary depending on manufacturer of machine.
5. Ultrasonographic
■ Still under development.
■ Largely useful only in calcaneus bone
■ Ultimately may help assess bone architecture as well as mineral density.

different techniques, even for the same technique using a different brand densitometer, the WHO uses the standard deviation from the mean peak bone density in young adults (age 25-40) for its diagnostic criteria: ***Normal*** bone density is defined as within one standard deviation of young adult normal BD. ***Osteopenia*** (low bone density) is defined as between 1 and 2.5 standard deviations below young normal BD. ***Osteoporosis*** is defined as 2.5 standard deviations below young normal BD.[4] Based on 1990 data, 15% of young adult women have osteopenia and 0.6% have osteoporosis. By age 70, 58% of women have osteopenia and 30% have osteoporosis; and by age 80, 70% have osteoporosis (see Figure 1).[3]

Major advances in the methods of measuring bone density have occurred in the last 15 years. The following methods are currently available (see Table 1):

- *X ray absorptiometry*—using an ordinary X ray of the hand, the density of which is then measured by a specialized technique.
- *Single photon absorptiometry* of the radius and ulna (now considered inadequate).
- *QCT*—Quantitative CT bone densitometry using the standard CT X ray equipment but using required special software and standards (only useful for vertebral BD but gives volumetric data).
- *Ultrasound methods*[5] are under development but have as yet not been deemed entirely reliable and are not yet approved by the FDA. Most will only be able to measure the density of the calcaneus (heel). The importance of this technique is that it may in fact be able to look at the architecture of the bone which together with the mineral content may more accurately reflect fracture risk. Cost effectiveness has not been evaluated as yet.
- *Dual-energy X ray absorptiometry (DEXA)* is the procedure of choice at the present time.[6] As is true for most of the other methods, it only gives

the mineral content of bone and cannot define the internal structure. It can be used for the wrist, spine, and hip. The dose of X ray is very low (1.5 mRems per procedure or less than 1/10th of the average chest X ray dose). The cost is usually about $200, although cost-effective management could reduce the cost to about $100. The equipment costs in excess of $70,000 and can do bone studies and body composition measurements.

Using DEXA bone densitometry, one can identify individuals at risk of developing osteoporosis as well as individuals who already have osteoporosis and are at high risk of fracturing. It is also possible to monitor therapeutic interventions without waiting for fractures to occur (see Table 2). It can identify individuals whose risk is so low that they never need further evaluation for this problem unless they develop a disease that directly affects bone mineral content. Bone density measurements give a fairly accurate assessment of the risk for fracture, with a continuous rise in risk as bone density declines (see Figure 2).

Appropriate interpretation of the bone densitometry is required for effective clinical use of this technique. For example: A 50-year-old newly menopausal woman who has a bone density in the osteopenic range at 1.5 standard deviations below young normal can be expected to enter the osteoporotic range within the next 10 years due to the usual 20% bone mineral loss seen in the first 10 years after menopause. Intervention by blocking the early postmenopausal loss will likely prevent osteoporosis. On the other hand, a 65-year-old woman who is more than 10 years postmenopausal and who has the same bone density is unlikely to enter the osteoporotic range, provided she does simple things like exercising moderately, eating adequate calcium and taking adequate vitamin D. Thus proper expert interpretation of the bone density readings, taking into account the patient's age and health circumstances, is critical to a true definition of the patient's risk of developing fractures. Using bone densitometry measurements, one can determine the level of mineral content in various age subjects in the population and thereby calculate the magnitude of the risk of future fractures in the spine, hip or wrist for each group.

Interventions that reduce the incidence of osteopenia in the younger age

Table 2. Clinical Use of Bone Densitometry

- Identify women at menopause who would benefit from antiresorptive treatment with bisphosphanates, calcitonin, or estrogens.
- To help women decide on the necessity for estrogen-progestin replacement therapy
- To monitor asymptomatic hyperparathyroid patients; low bone density is an indication for surgery in this disorder
- Repeat after 1 or 2 years of therapy to assess response to treatment. To find the subgroup of patients on hormone therapy who continue to lose bone mass
- To monitor therapy in patients with osteoporosis
- In patients on chronic therapy that reduces bone mass: steroids, GNRH, dilantin and heparin.
- In patients who have estrogen deficiency at an early age: those with amenorrhea or anorexia or ovarian failure.

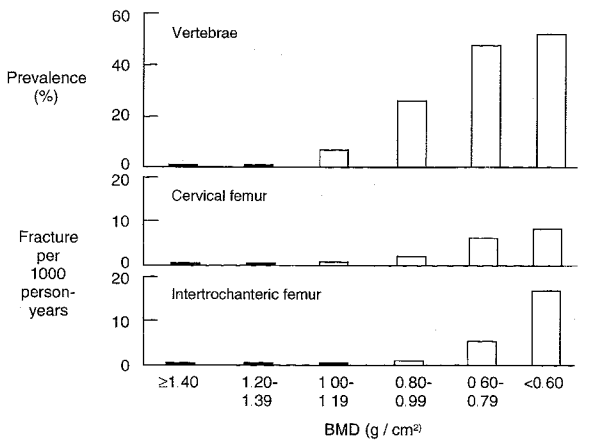

Figure 2. Occurrence of vertebral and proximal femoral fractures at various levels of vertebral and proximal femur bone mineral density (BMD). Data are from a random sample of women in Rochester, Minnesota, and from a sample of patients from the same population with hip fractures or vertebral fractures.
Taken from Riggs & Melton. Osteoporosis. *N Engl J Med* 1986;314:1678.

groups are likely to reduce the incidence of osteoporotic fractures in the older age groups.

Other Tests to be Done Prior to Therapy

Low bone density alone is suggestive of, but not synonymous with, osteoporosis even if it is in the range of the WHO criteria for osteoporosis. Any cause of loss of bone mineral or poor mineralization of bone will result in similar density measurements. For example, individuals who have vitamin D deficiency have osteomalacia, *not osteoporosis*, but have low bone mineral density. Treatment with adequate vitamin D will correct the problem. In our own data of 100 peri- and postmenopausal women found to have low bone density, about 3% had low levels of vitamin D. In the very elderly, this may be even more common. Measurements of vitamin D would identify these individuals. In older individuals, especially those over 80 years, any compromise of renal function may reduce the efficiency of converting dietary vitamin D into the active form 1,25-dihydroxycholecalciferol. In such instances, measurement of the latter compound is appropriate. Treatment for these individuals may require the administration of calcitriol rather than ordinary dietary supplements of vitamin D. The cost of this medication is much higher than vitamin D supplements and may have a higher risk of causing hypercalcemia and renal stones. Therefore, it should not be used in people who just require more ordinary vitamin D.

Hyperparathyroidism is a common cause of secondary bone loss. Its highest incidence is in postmenopausal women.[7] This disorder is asymptomatic in about 55% of affected individuals. Ordinarily, it is associated with hypercalcemia which would be found by simply doing a routine blood multichemical analysis. In the course of evaluating women with presumed postmenopausal low bone density, we have found that about 10% of asymptomatic individuals who had bone density screening were found to have an elevated parathyroid level without hypercalcemia. This may reflect an early form of hyperparathyroidism, or it may have some other undetermined etiology. Elevated parathyroid hormone levels are also found in individuals who have vitamin D deficiency.

It is important for the physician to identify individuals who have secondary loss of bone mineral due to other diseases and not to label all low bone density as postmenopausal osteoporosis. Therefore, prior to treating anyone with drugs designed for the management of osteoporosis, these secondary causes should be ruled out (Table 3).

The Use of Bone Markers *(see Tables 3 and 4)*

In people who have low bone density, especially if they meet the WHO criteria for osteoporosis, or in women who have not yet experienced early postmenopausal bone loss, one needs to know more about the skeletal system. Bone is active tissue undergoing constant removal and replacement. Osteoclasts resorb bone and then are replaced by osteoblasts which normally refill the cavity left by the osteoclasts. In young adults, probably up to the age of 40, there is a perfect balance between bone resorption and bone formation, resulting in no loss or gain in bone substance. After age 40, in both men and women, bone resorption exceeds bone formation by about 0.5 to 1% per year, resulting in the known age-related loss. In

Table 3. Clinical Use of Bone Markers, Vitamin D, and PTH Levels

- In individuals who have ostopenia or osteoporosis, to rule out osteomalacia and hyperparathyroidism
- To monitor effect of treatment—short-term (before significant change in BD)
- To identify bone turnover rates (high or low)
- To identify and treat perimenopausal women with mild osteopenia (bone density of only 1 SD below young normal) who have high bone turnover rate and are therefore likely to develop osteoporosis

women, during the first 10 years after menopause, the yearly loss rises to 2-5% per year, largely due to the increase in bone resorption always seen after loss the of sex steroids.

An individual's bone density is the result of genetic background and lifelong factors such as age at puberty and menopause, and level of exercise and amount of calcium intake during childhood, adolescence, and adulthood. At the time of diagnosis of low bone density, it would be helpful to know whether there is active rapid bone loss or whether the bone density reflects earlier loss. In the past, to distinguish these situations, a bone biopsy was done after two timed administrations of tetracycline for morphometry. This method is less than ideal because it is invasive and expensive. It can only be used in bone sites not directly in the area of interest, and there are marked discrepancies in its interpretation.

More recently, bone markers that reflect bone turnover have been identified. These include blood levels of bone alkaline phosphatase and osteocalcin which measure activity of the osteoblasts that are rebuilding bone. Urinary measurements of specific breakdown products of the underlying bone matrix have also been developed. These include urine n-telopeptide, pyridinoline, and deoxypyridinoline. Measurements of these markers may reflect bone turnover states in the low bone density patients, suggesting more urgent treatment for those having high turnover rates since they are likely to lose bone rapidly. They can also be used early in a treatment program to monitor its effectiveness. They do *not* identify individuals who have low bone density in the first place. These tests cannot replace bone densitometry. Their cost effectiveness and correct use will have to await further study.

Prevention and Treatment Strategies

Strategies for the management of patients with osteopenia to prevent the development of osteoporosis and those who have frank osteoporosis with fractures are similar. Distinction must be made between caring for the ***large number*** of patients at risk of developing osteoporosis from those who ***actually have clinical disease.*** The risk-benefit ratio of treatments is different for prevention than it is for treatment of patients with fractures (Tables 5, 6, and7).

Table 4. Bone Markers

Bone Formation or Osteoblastic Activity	
Bone alkaline phasphatase	(bAP)
Osteocalcin	(BGP)
Propeptides of type I collagen	(S-PICP)
Bone Resorption or Osteoclastic Activity	
Urinary	
- Hydroxyproline	(DHPr)
- Pyridinoline crosslinks	(D-Pyr)
- Deoxypyridinoline crosslinks	(D-Pyr)
- N-terminal telopeptide	(NTx)
Serum	
- Terminal pyridinium crosslinked telopeptide of type I collagen (ICTP)	
- Tartrate-resistant acid phosphatase (TRAP) (Lysozymal enzyme produced by osteoclast)	

Exercise and Physical Therapy

Bone mineralization is dependent on physical stress on the bone. Exercise is the key to this. In individuals who are put on bed rest, or in a limb that is paralyzed, there is rapid bone mineral loss. Weightlessness, as in space travel, results in major loss of bone mineral. Exercise reverses that process. Exercise during adolescence is crucial to achieve maximum bone density. Even in older adults, exercise has been shown to improve bone density.[9] Exercise in the elderly will improve muscle strength, improve balance and prevent falls which are a major cause of hip fractures.[10]

In the Rancho Bernardo study of fractures, lifetime leisure exercise was reported to result in increased bone density.[11] Exercise increased bone density but only over a long period of time. Jaglal et al reported that women who had heavy activity jobs for 20 years or more had a reduced risk of hip fracture.[12]

A key treatment for individuals who have fractures as well as those who have osteoporosis based on bone density measurements is exercise. A specific program should be developed for each individual by a Physiatrist (Rehabilitation MD) who will refer the patient to a physical therapist for training. Exercises randomly assigned without careful assessment of the individual's particular problems may result in further fractures. Appropriate exercise can improve muscle strength which then increases the mechanical force applied to the bone, and, in turn, can increase bone density.

Role of Calcium

Calcium, an essential element, is the main supporting substance of bone. To have good bone density, individuals must have adequate intake of calcium *lifelong, especially during the years of bone formation during adolescence.* Even during adult life, there is a daily loss of calcium via the intestine. If this is not constantly replaced, calcium will be removed from the bones to maintain blood calcium levels which are very strictly controlled to maintain normal cellular function throughout the body. Approximately 300 mg of calcium are lost each day. To replace it, an individual must eat about 1000 mg of calcium because only 30% is absorbed (in very old individuals, absorption is even lower, resulting in higher daily recommendations as high as 1500 mg in women over age 70).

A population study in two areas of Yugoslavia showed that the incidence of fractures was much higher and occurred much earlier in a district whose standard diet was low in calcium intake as compared to a district that had high dietary calcium intake.[13]

Adequate calcium intake is essential to management of osteoporotic individuals. In older individuals who did not have osteoporosis, the incidence of nonvertebral fractures was reduced significantly by the administration of modest doses of calcium—500 mg per day—together with 400 units of vitamin D.[14]

Several retrospective studies have suggested that excessive intake of calcium as supplements or in the form of milk may actually increase the risk of fracture. In the Nurses Health study in which 78,000 nurses were followed without intervention, higher calcium intake in excess of 450 mg/day doubled the risk of hip fractures.[15] High intake of calcium may in fact reduce parathyroid hormone levels, blocking the effect of low-dose parathyroid hormone in activating osteoblasts. In the Study of Fractures, high calcium supplemental levels doubled the risk of fractures.[16]

Current recommendations, from the most recent NIH consensus

Table 5. Cost of Monthly Supply of Drugs Used for the Prevention or Treatment of Osteoporosis (Average Wholesale Cost)

Drug	Dose/Day	Average Wholesale Cost/Month
Vitamin D	400 units	$0.30 - 0.75
Calcium Carbonate	1000 mg	2.25
Estrogens		
pills	1 0 mg - 0.625 mg	10.00
patches	0 05 mg/week	20.00
Estrogen/Progestin Combined	0.625/2.5	17.60 - 19.20
Alendronate	10 mg	52.00
Etidronate	400x14d/3 mos	19.00
Calcitonin		
injection	100 units	96.00
spray	100 units	100.00
Fluorical (low-dose fluoride/calcium)	8.4/325 mg tid	9.90

conference, are for all adults to take in about 1000 mg of calcium each day, either in their diet or by taking calcium carbonate (to be taken with food) or calcium citrate supplements (well absorbed even without food). A higher goal of 1500 mg per day is recommended for postmenopausal women who are not receiving estrogen replacement therapy.[17]

Vitamin D

Calcium absorption requires vitamin D. This can be manufactured in the skin by exposure to sunshine or through the diet. Deficiency of this vitamin has become much more common for two reasons: (1) The widespread use of taking many individual vitamins such as C or E has stopped people from taking a true multivitamin. (2) In individuals who use sunscreen, conversion of cholesterol to vitamin D in the skin does not occur. Therefore, people who live in northern climates, or who are shut indoors, or who carefully use sunscreen require vitamin D supplements. The daily requirement is 400 units. This can be found in a glass of milk or in any standard multivitamin preparation. A vitamin D dose of 700 IU per day prevented bone loss in the spine and the femoral neck in healthy postmenopausal women.[18] The liver stores vitamin D; therefore, it is not essential to have it every day. Normal kidney function is needed to convert vitamin D into its active metabolite 1,25-dihydroxycholecolciferol. In people with kidney failure, the final metabolite needs to be provided (as calcitriol). Many very old people have some degree of kidney failure and have difficulty making this metabolite.

Deficiency of vitamin D can be identified by measuring 25-hydroxycholecalciferol in the blood. This substance reflects the intake or manufacture of vitamin D and is stable. In subjects with renal insufficiency, measurement of 1,25-dihydroxycholecalciferol will identify those unable to metabolize vitamin D. There is no need to measure these routinely, but if an individual has very low bone density or has frank osteoporosis, knowing that his or her vitamin D is low can help in treating that individual. Low bone calcium in vitamin D deficiency is *not* osteoporosis but osteomalacia, an altogether different problem that results in softer bones but not necessarily easily fractured bones. Treatment with vitamin D will restore the bone to normal.

Studies of femoral neck osteoporosis in elderly men (over age 70) found that low levels of vitamin D were significantly related to fractures.[19] In a three-year study of 300 community-dwelling seniors, Tilyard reported a reduction of about 60% in the hip fracture rate in the group treated with vitamin D and calcium as compared to the group given only calcium.[20]

Table 6. Prevention of Osteoporosis

- exercise
- calcium intake 1000 mg/day
- vitamin D 400 units/day
- no smoking
- no excess alcohol
- bone density testing in women aged 40-50
- consider estrogen if osteopenic by WHO criteria
- alternative: alendronate 5 mg/day
- alternative: raloxifene 60 mg/day

Table 7. Treatment of Osteoporosis

- analgesics
- physical therapy
- calcium 1000 mg/day (1500 in women >75 years)
- vitamin D 800 units/day
- pharmacologic therapy:
  (1) estrogen replacement therapy equivalent to 0.625 mg/day equine conjugated estrogens
  (2) alendronate 10 mg/day
  (3) calcitonin: Nasal CT 100-200 IU/day; SQ 100-200 daily or 3 times/week

The currently recommended dose of vitamin D is 600-800 units per day,[17] 400 units of which are usually found in any multivitamin pill. Since subjects will likely get some vitamin D in food products or from the sun, most are actually getting approximately 600-700 units per day. Older individuals who have renal diseases may require supplementation with the active form of vitamin D—1,25-dihydroxy vitamin D (calcitriol).

Ovarian Hormone Replacement

In women who are identified as having a bone density lower than 1.5 or 2 standard deviations below young normal mean bone density, the early postmenopausal bone loss (estimated to be as high as 20% of total bone mineral) will result in osteoporosis by WHO criteria before they reach their 70th birthday. Estrogen hormone replacement will prevent this from occurring. In fact, during any of the early years after menopause, treatment with estrogens will stabilize bone mineral and block loss of bone matrix. This has been shown to reduce fracture rates by 50% or more.[21,22] Estrogens have been used for this purpose for more than four decades. Both oral and transdermal estrogens have been shown to prevent bone resorption. Many preparations of estrogens have been FDA-approved for the prevention and treatment of osteoporosis. The PEPI trial in which 875 women were randomized to placebo, estrogens (conjugated equine estrogens at 0.625mg/day) alone, or estrogens with cyclic or continuous medroxyprogesterone acetate or micronized progesterone showed increased bone density in all groups taking estrogen. No additional bone effects were noted in the groups who took progestational agents in addition to the estrogens.[23] In the CHART study, 1265 postmenopausal women were randomized to placebo, conjugated estrogens or conjugated estrogens with norethindrone acetate. The addition of the progestin resulted in a further increase in bone density.[24] Both these studies documented the beneficial effects of estrogen replacement therapy on risk factors for coronary artery disease. Micronized progesterone is identical to the progestin made by normal ovaries. The synthetic progestins are mostly derivatives of testosterone. One of the most androgenic ones is norethindrone, whereas medroxyprogesterone acetate is very minimally androgenic. Androgens have, in the past, been thought to increase bone density.

Estrogen is particularly useful in preventing the early postmenopausal bone mineral loss. In order to prevent fractures, however, therapy must be long-term because whenever estrogen treatment is stopped, the same loss of bone mineral as in the early postmenopausal period is seen. Low-dosage estrogen (half of the usual dosage) can also maintain bone density but has not yet been proven to reduce fractures directly.[25] In older individuals who are more than 15 years postmenopausal, low-dose estrogen may in fact be sufficient due to reduced levels of sex hormone-binding globulins, resulting in higher free estrogen levels and more effective amounts of the free hormone.

Estrogen has been the main form of therapy for osteoporosis, in use for at least 50 years. Although fear of an increase in breast cancer with the use of estrogen often results in reduced compliance, the data do not show a large effect on the risk of breast cancer even with long-term estrogen use. Recently, in a study of women with first-degree relatives who had breast cancer, there was no evidence the women had an increased risk of getting breast cancer while on estrogen replacement. In fact, the mortality rate was lower in those who developed breast cancer while on estrogen replacement than in those who developed breast cancer and had not been on estrogen.[26]

Estrogen replacement therapy has the additional probable benefit of reducing the risk of coronary artery disease by 40-50%. The Women's Health Initiative that concludes in 2004 will almost certainly demonstrate that this is so. Both

the prevention of osteoporotic fractures and the prevention of heart disease require continued replacement with estrogens. The true risks of this long-term therapy need to be measured.

Selective Estrogen Receptor Modulators (SERMs)

These are interesting drugs that activate estrogen receptors in some tissues but block their actions in others. An example is tamoxifen, largely used in the treatment of breast cancer, which blocks estrogen effects on the breast but stimulates estrogen receptors in the uterus, bone and lipid pathways. Tamoxifen has a positive effect on bone density[27] but has not been shown to decrease fractures.

Raloxifene is a new SERM which has just been released for the prevention of osteoporosis. The data thus far show an increase in bone density of about 1-2% per year which is about half of what one sees with standard estrogen therapy. However, this drug appears to have little or no effect on the uterus and from preliminary data may reduce the frequency of breast cancer. The number of women treated to date and the length of time of treatment is insufficient as yet to be certain that these results will continue to be significant over time.[28]

Several other drugs have recently been approved for the prevention and/or treatment of osteoporosis. All these drugs block bone resorption, preventing loss of bone mineral and the underlying bone matrix. Most have been used for only a few years (usually less than 10), and their long-term effects are as yet unclear.

Bisphosphonates

A number of bisphosphonates are under study for the treatment of osteoporotic fractures. Alendronate, the first to be released for this use in the United States appears to be a very potent drug. Its use has resulted in a 3-4% increase in bone density every year it's been taken for the 4 years of use reported thus far. It has been shown to reduce the risk of fracture in individuals who already have an osteoporotic fracture and in subjects susceptible to fractures. In fact, the more fractures the individual has, the greater the percent reduction of fracture risk.[29] The side effects have been minimal with an incidence of gastrointestinal problems of about 1-2%. Patients must be cautioned to remain upright after taking their medication because esophageal irritation and erosion are the major side effects. For any absorption to take place, the drug must be taken on an empty stomach at least 30 minutes before eating.

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Alendronate and probably many other bisphosphanates remain intact in the bone matrix and can be released whenever bone resorption occurs. The long-term risks of this are as yet unknown since only about 10 years of studies are presently available. The use of this drug for the prevention of osteoporosis therefore requires caution. A 45-year-old woman who has low bone density but is not having clinically significant fractures has a life expectancy of about 40 years. The effect of the continued presence of the bisphosphanate in her bones is unknown. Therefore, at present, alendronate should be considered an excellent drug for treatment of osteoporosis but its use in prevention should be carefully evaluated in each patient. In women who are unable to take estrogens, this may be the drug of choice.

Etidronate, which has been used for many years for the treatment of Paget's

disease, has been shown to prevent the menopausal loss of bone mineral when given intermittently, that is, 400mg/day for 14 days every 3 months.[30] The advantage of this therapy is that it is far less costly (see Table 5). However, this drug has not been approved for use in the treatment or prevention of osteoporosis by the FDA because of a paucity of prospective data in patients who have osteoporotic fractures. The main problem with this drug is that when used continuously or in high doses it may block osteoblastic activity and reduce mineralization of the bone. This drug appears very useful for the prevention of secondary osteoporosis in patients on chronic steroid therapy as reported by Adachi et al.[31] Most of these patients are on many drugs for their underlying disorder. Taking etidronate for 14 days every 3 months improves compliance.

Calcitonin

Calcitonin is a natural substance made by the endocrine glands in most animals as well as humans. It is a protein and must therefore be administered by injection or by nasal spray.[32] It is absorbed across the mucous membranes. Widely used in Europe for the prevention of osteoporosis, the nasal spray was only released a few years ago in the United States for treatment of osteoporosis. The injectable form is more reliably absorbed, but few patients are willing to use alternate-day or daily injections for long periods of time. It can prevent the loss of bone mineral in the early postmenopausal woman. It has also been shown to reduce the risk of fracture in patients who already have fractures. The main problem with this drug is its high cost.

This is the only treatment for osteoporotic fractures that appears to reduce pain. This can be quite dramatic in some patients although the nasal spray has not seemed to be as effective, perhaps because of dosage differences.[33]

Fluoride

Fluoride has been shown to increase bone formation. Its use to prevent osteoporosis is not well established. Fluoride, in fairly high doses, was an early drug used for the treatment of osteoporosis. Careful analysis of the data showed that, whereas the bone appeared denser on X rays, it was in fact more brittle and in three-year trials the fracture rate in the third year was higher in the patients on fluoride than in the placebo group.[34]

More recently, Pak et al[35] have shown that low doses of fluoride may in fact be beneficial. Further multicenter studies need to be completed before this drug can be recommended for this indication. The major benefit would be that since fluoride stimulates osteoblastic activity rather than blocking bone resorption, it may in fact improve bone formation. This would be particularly useful when combined with an antiresorptive agent. Its place in the treatment of osteoporosis must await further studies.

Between 30 and 40 years ago, most American communities began to fluoridate their water supplies. Fluoride is one substance which in low doses may influence osteoblastic activity. The effect of water fluoridation on bone density is unknown but could have a significant influence on the future prevalence of osteopenia and osteoporotic fractures. With the more recent trend to use bottled unfluoridated water, the public may be inadvertently preventing such a beneficial effect.

Parathyroid Hormone (PTH)

Parathyroid hormone plays a major role in bone metabolism. At high levels, it causes bone resorption and is associated with loss of bone mineral as in subjects who have hyperparathyroidism. Parathyroidectomy improves bone density in primary hyperparathyroidism.[7] Low levels of parathyroid hormone, however, are helpful in bone formation. In fact, suppression of PTH by high calcium intake or hypercalcemia may increase the risk of fractures. PTH is not presently clinically available. However, studies of its possible value are in progress. It will probably be useful but may

have to be administered intermittently. The product is a protein and will require parenteral administration.

Removal of Agents That Cause Loss of Bone

Cigarette smoking and excess alcohol intake result in loss of bone mineral. Excessive use of caffeinated drinks in the absence of milk may also result in loss of bone mineral. Alcoholism is a major cause of osteoporosis in adult men.[36]

Treatment for Other Disorders May Result in Osteoporosis

Many drugs cause loss of calcium from bone. The main culprit is glucocorticoids when used in pharmacologic doses as in the treatment of asthma or allergic disorders, or as treatment for lupus erythematosus, etc. Glucocorticoids cause loss of calcium from bone by many mechanisms. First of all, they have a direct effect on bone. This effect may be blocked by progesterone. No study of this has been reported. Glucocorticoids prevent absorption of calcium from the intestine. This can be overcome by adding vitamin D at higher than usual doses (approximately 400 units for every 10 mg of prednisone), together with larger amounts of calcium intake (1500 to 1800 mg per day). The major danger is that increased absorption of calcium may result in increased renal excretion of calcium which can put the individual at risk for renal stones. Monitoring urinary calcium content and adjusting the doses of vitamin D and calcium can prevent this major complication. The use of some antiepileptic agents such as dilantin can also change the requirements for vitamin D.

Management of Pain

Analgesics are obviously necessary for patients who have pain. In osteoporosis, pain only occurs in association with fractures. Vertebral fractures in the lumbar region may be accompanied by pain lasting for a long time. The lumbar vertebrae support the body, and any motion of the upper body may alter the alignment of these bones, resulting in pain. Fractures of the thoracic vertebrae are rarely associated with pain, possibly because the vertebral bodies are stabilized by the rib cage. Patients who develop major kyphosis often have no pain whatsoever even though their vertebral bodies have collapsed. Some of the pharmacologic agents used to treat osteoporosis appear to have analgesic effects, particularly calcitonin,[33] although we have seen it as well in secondary osteoporosis treated with etidronate and other bisphosphonates.

Individuals who have pain from other disorders such as osteoarthritis may find it difficult or impossible to exercise. Water exercise is useful for these individuals but will not increase bone mass. Pain must be managed prior to effective physical therapy, or exercise can be instituted.

The use of support garments may be helpful, but their utilization may result in further weakening of the associated muscles.

Summary

Osteoporosis has become a major problem in an aging population. Its prevalence may reach almost 100% in nonagenarians. The prevention of osteoporosis depends on lifetime changes, starting in childhood, in exercise, calcium and vitamin D intake as well as in identifying those individuals most at risk. Bone densitometry is currently the best measurement of an individual's risk of having fractures. It can be used to find those individuals in whom further intervention is warranted.

Of the available pharmacologic treatments, estrogens have had the longest trials and reduce fracture rates by 50%. Recently alendronate, calcitonin, and raloxifene have been added to the armamentarium for prevention or treatment of this disorder.

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CME QUESTIONS: TEST #049802S

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Instructions

After reading the article, "The Management of the Patient with Osteoporosis—A Modern Epidemic," select the best answer to each of the following questions. In order to receive 1 CME credit, at least 7 of the 10 answers must be correct. Estimated time for this activity is one hour. CME credits are distributed on a yearly basis.

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1. Osteoporosis and osteomalacia can be differentiated by:

a) bone densitometry
b) blood vitamin D levels
c) age of patient
d) dietary history
e) all of the above

2. The best way of making a diagnosis of osteoporosis is:

a) X ray of the spine and hip
b) ultrasonogram
c) urine deoxypyridinoline
d) dual-energy X ray absorptiometry (DEXA)
e) none

3. The daily calcium requirement for adults aged 25-50 years is:

a) 800 mg
b) 1,000 mg
c) 1,500 mg
d) 600 mg
e) 400 mg

4. Treatment of osteoporosis with estrogens, alendronate or calcitonin acts by:

a) increasing bone formation
b) decreasing bone resorption
c) both of the above
d) none of the above

5. The age-related loss of bone mineral content starts at age:

a) 50
b) 60
c) 30
d) 40

6. Women are more likely to have osteoporosis than men for all the following reasons except:

a) have lower bone density than men at all ages
b) are more likely to have had less strenuous exercise as teenagers
c) lose their sex steroids as a normal event long before old age
d) are more likely to have the genetic background for osteoporosis
e) are more likely to have less calcium in their diet

7. Blood and urine bone markers measure the activity in bone:

a) of bone resorption and formation
b) can be used to make the diagnosis of osteoporosis
c) and help rule out osteomalacia
d) none of the above
e) all of the above

(CME QUESTIONS CONTINUED ON PAGE S109)

CME TEST FORM
AJMC Test #049802S

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On the whole, how do you rate the information presented in the article?

____ excellent ____ good ____ fair ____ poor

Is the information presented useful in your practice?

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Program Evaluation

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(CME QUESTIONS CONTINUED FROM PREVIOUS PAGE)

8. Alendronate is used to treat osteoporosis. It is a:
a) steroid
b) hormone produced by the thyroid
c) calcium complex
d) bisphosphanate

9. The only medication for osteoporosis that is also an analgesic is:
a) fluoride
b) calcium
c) estrogens
d) alendronate
e) calcitonin

10. A 69-year-old woman has a sudden onset of pack pain. It is most likely due to:
a) collapse of L4 vertebral body
b) generalized low bone density
c) collapse and wedging of T3 vertebral body
d) Rheumatoid arthritis
e) Paget's disease of the bones