Diagnosis and Management of Osteoporosis in Postmenopausal Women: Clinical Guidelines

Pierre J. Meunier, MD, Pierre D. Delmas, MD, Richard Eastell, MD, Michael R. McClung, MD, Socrates Papapoulos, MD, Rene Rizzoli, MD, Ego Seeman, MD, and Richard D. Wasnich, MD, the International Committee for Osteoporosis Clinical Guidelines

ABSTRACT

The authors, all physicians involved in clinical research on bone and practicing clinicians, propose practical guidelines for identifying persons with osteoporosis or those at high risk of developing the disease and for managing patients who may benefit from therapy. These guidelines are based on an analysis of peer-reviewed articles published before November 1998. A flowchart of women who might benefit from treatment is provided, including clinical presentation (recent fracture of the spine, hip, or other bone or no fracture; risk factors for osteoporosis); relevant investigations (bone mineral density measurement and laboratory tests required for the differential diagnosis); and therapeutic management (general measures such as calcium and vitamin D supplemenation and specific pharmacologic interventions such as estrogen, bisphosphonates, intranasal calcitonin, raloxifene, fluoride salts, and other compounds that have been assessed in randomized clinical trials). The strongest evidence for antifracture efficacy (reduction of vertebral and nonvertebral fracture risk) was observed with alendronate. Key words: osteoporosis, bone mineral density, fracture, postmenopausal.

INTRODUCTION

As physicians involved in clinical research on bone and practicing clinicians who routinely see patients with osteoporosis, we are often asked by colleagues for practical guidance on how to identify women with osteoporosis or at high risk of developing the disease, as well as how to manage patients who may benefit from...
CLINICAL THERAPEUTICS

therapy. The present guidelines provide an up-to-date summary based on an analysis of peer-reviewed articles as of November 1998. Research on osteoporosis is ongoing, and future developments will no doubt be incorporated into subsequent versions of these guidelines.

The Clinical Challenge: Frequency and Consequences of Osteoporotic Fractures

Osteoporosis is a systemic skeletal disease characterized by low bone mineral density (BMD) and microarchitectural deterioration of bone tissue, leading to bone fragility and increased fracture risk. It is especially prevalent in older postmenopausal women. If untreated, more than half of white women will experience an osteoporotic fracture during their lifetime. The burden of pain, physical disability, and reduced quality of life among these women represents a major public health problem.

For white women, the cumulative lifetime risk for fractures includes a 16% risk of an painful vertebral fracture, 15% risk of Colles’ (wrist) fracture, and 16% risk of hip fracture. When all fractures are considered, the lifetime risk of experiencing a fracture is >50%. Many women who have 1 osteoporotic fracture will experience further fractures, partly because prior fracture is itself an important independent risk factor for future fracture. Furthermore, women with very low BMD have much higher risks than the average, and many of them will experience fractures if untreated.

Although all fractures are debilitating to some degree, hip fracture is the most serious consequence of osteoporosis. Women with hip fracture are 2 to 4 times more likely to die within 12 months of the event as are women of the same age without hip fracture in the general population, but the extent to which these deaths are related to comorbid conditions rather than hip fracture remains controversial. In women surviving 12 months after suffering a hip fracture, severe functional declines are observed. In one prospective study of women with hip fractures, a respective 50%, 70%, and 87% did not recover the ability to walk independently, transfer from one place to another independently, and climb stairs independently. Other studies based on recall reported that depending on the activity, between 20% and 60% of women with hip fracture failed to recover baseline function within 6 to 12 months after the event. A Scandinavian study reported that 31% of surviving hip-fracture patients were bedridden 6 years later, compared with 1.5% of the control group, and that only 9% of the fracture cases could walk outdoors by themselves, compared with 55% of the control group.

In one report, hip fractures were responsible for more hospital bed days among women after age 45 than were myocardial infarction, breast cancer, chronic obstructive pulmonary disease, or diabetes. Moreover, hip fractures represent only a small part (~10%) of the fractures and use of outpatient services related to osteoporosis, with as few as 16% of fracture-related hospitalizations among the elderly associated with hip fractures.

Vertebral fracture is the most common osteoporotic fracture and occurs earlier in life than hip fracture. Like hip fracture, vertebral fracture is associated with considerable morbidity. The acute pain can range from mild to intolerable, and chronic pain can persist for years. Among women with symptomatic vertebral fracture and
P.J. MEUNIER ET AL.

chronic pain, 60% to 87% reported problems with carrying, lifting, walking, doing housework, and shopping. Although less common, difficulties traveling, dancing, and athletic activities were rated as important. Approximately two thirds of all vertebral fractures are not recognized clinically, but both diagnosed and undiagnosed vertebral fractures are associated with pain and impaired physical function. Declines in physical function and changes in appearance (kyphosis and height loss) contribute to social isolation and loss of self-esteem, impairing quality of life.

The incidence of wrist fracture increases rapidly around menopause. Thus wrist fracture represents the earliest effect of osteoporosis in some patients and, like other low-trauma fractures, indicates an increased risk of future fracture. Most studies have estimated that 8% to 10% of patients experiencing wrist fracture are hospitalized, but one study found that the percentage increased to 76% after age 85. Another sometimes severe consequence of wrist fracture is algodystrophy (reflex sympathetic dystrophy); <10% of patients were affected in most surveys, but the number has been reported to be as high as 30%.

Thus both spinal and nonspinal osteoporotic fractures contribute to declines in physical function and quality of life, and the severity of these declines increases with the number of fractures. Women who have had spinal or nonspinal fractures are 2 to 6 times more likely to report difficulties performing activities of daily living than are those without fractures. Furthermore, decreases in physical function often lead to an increased risk of falls and fractures and to the fear of falling, which further restrict activities and independence. The need for chronic care in the home or nursing home, medications, and rehabilitation and the lost productivity of those caring for these elderly patients at home further add to the very substantial burden imposed by osteoporosis. These burdens will increase dramatically in the coming decades because of the growing population of elderly persons.

BMD peaks during the third decade, declines rapidly around menopause, and continues to decrease thereafter. As a result, in the absence of treatment, postmenopausal women commonly develop osteoporosis and fractures in later life (Figure 1). On average, women lose between one third and one half of their peak BMD in the course of their lifetime. This severely compromises bone strength at later ages, when fracture can result from minimal trauma. A World Health Organization (WHO) study group has defined osteoporosis as a BMD ≥2.5 standard deviations below the young adult mean. Patients with a BMD between 1 and 2.5 standard deviations below the young adult mean are classified as having low bone mass, or osteopenia. The number of standard deviations above or below the mean for young women is referred to as the T-score (Figure 1). By WHO definition, ~95% of young women have BMD values between −2.0 and 2.0; many untreated older women have lower values.

Extensive epidemiologic data demonstrate that fracture risk increases progressively as bone density decreases (Figures 2 and 3). Because of the continuous relationship between BMD and fracture risk, there is a much greater range of fracture risk than is implied by the use of 3 categories (ie, normal, low bone mass, and osteoporosis) based on T-score.

Within the category of osteoporosis, for
example, a woman with a T-score of -4.0 has a greater risk of fracture than one with a T-score of -2.5. Other risk factors such as age, preexisting fracture, thinness, and high bone turnover may contribute to increased risk independent of low BMD and should be considered when making decisions about treatment.10-13,46

The Aim of Therapy

Effective therapies for treatment and prevention of osteoporosis with good safety profiles are now available. The aim of such therapy is to reduce osteoporosis-related morbidity and mortality by safely reducing the risk of fracture. Consequently, an important clinical goal is to identify patients with osteoporosis or at high risk of developing the disease. Although fractures tend to occur relatively late in life, they result from the bone loss and microarchitectural deterioration that occur from menopause onward. The purpose of therapy is to maintain or increase bone strength to prevent fractures throughout the patient's lifetime.

Figure 4 illustrates our approach to identifying candidates for treatment, which is similar to that in osteoporosis guidelines published by other authors.24,47 The National Osteoporosis Foundation guidelines47 are somewhat more liberal than ours, basing therapeutic decisions on a T-score cutoff of -2.0. Our guidelines also differ from others in making a distinction between prevention and treatment. Our rationale is that certain therapies are approved only for treatment in some countries and for both prevention
Figure 2. The relationship between bone mineral density (BMD) and fracture risk, based on a doubling of risk with each SD decrease in BMD. A T-score of 0 represents the mean BMD for young healthy women and is assigned a relative risk of 1.0 as the reference value. T-scores between −1.0 and −2.5 indicate low bone mass, and values below −2.5 indicate osteoporosis.43

Figure 3. Incidence of hip fracture per 1000 woman-years in 3 categories of femoral-neck BMD, using World Health Organization definitions of osteoporosis and osteopenia.43 Incidence increases in proportion to that of the 3 corresponding categories in Figure 2. Fx = number of women with hip fracture; N = number of women. (Reprinted with permission from the EPIDOS study, Schott et al.44)

and treatment in others. The aim of treatment is to provide a maximum benefit in terms of increased BMD and decreased fracture risk in women who are already at high risk, whereas the goal of prevention is to maintain BMD and thereby avoid an increase in fracture risk.

CLINICAL PRESENTATION

Postmenopausal women who require management of osteoporosis may present with ≥1 of the following: (1) evidence of a vertebral fracture; (2) after a hip fracture; (3) after another type of fracture (eg, wrist fracture);
Figure 4. Clinical flowchart of the presentation, investigation, and management of postmenopausal osteoporosis. BMD = bone mineral density, HRT = hormone replacement therapy. *Indicates a fracture resulting from a fall from standing height or lesser trauma and excludes fractures of the skull, facial bones, and digits. †Benefits may be limited if life expectancy is short (particularly if age is >80 years), unless additional risk factors are present or BMD is < -3.5. ‡For example, thin body build, high markers for bone turnover, BMD between -2 and -2.5, and maternal hip fracture.
(4) risk factors for osteoporosis; and (5) concern about the possibility of osteoporosis.

Most patients with osteoporosis are asymptomatic. Many patients who have experienced ≥1 fracture will have continuing pain, impaired mobility, and fear of further fractures that may reduce their quality of life. Moreover, such patients have often lost 30% to 50% of their peak bone mass. Although effective therapy can substantially reduce the risk of further fractures, the risk remains appreciable. It is preferable to intervene early in the process of bone loss and thus reduce the risk of the first fracture. This is now achievable, because even in the absence of previous fracture, the diagnosis of osteoporosis or high risk for developing osteoporosis can be made by measuring BMD.

Patient management varies somewhat according to the mode of presentation.

**Vertebral Fracture**

Physicians should be alert for features suggesting vertebral fracture in women aged ≥65 years, such as kyphosis, height loss, and acute or chronic back pain. Many vertebral fractures are not associated with acute symptoms. Because some degree of kyphosis and height loss may occur in the absence of osteoporosis, it is important to confirm the presence of a vertebral fracture on lateral spine roentgenograms.

**Hip Fracture**

With the exception of hip fractures caused by severe trauma, most hip fractures occur after a fall and are due to osteoporosis. In addition to having often-severe osteoporosis, patients who have suffered a hip fracture are generally frail and prone to falling, which places them at risk for further fractures. Therefore, patients who have experienced hip fracture should be managed actively, with the possible exception of those with a short life expectancy. Contributing causes, such as vitamin D deficiency, protein malnutrition, and other illnesses, are common in this population.

**Other Types of Fracture**

Wrist fracture is common. It tends to occur at a somewhat younger age than vertebral or hip fracture and hence often represents the first clinical expression of osteoporosis. Wrist fracture justifies BMD measurement to confirm the presence of osteoporotic disease.

Other types of fracture, as of the humerus, rib, or pelvis, are also common in patients with osteoporosis and require further assessment.

**Risk Factors for Osteoporosis**

Figure 4 delineates the major risk factors for osteoporosis. White and Asian women are at greater risk for osteoporosis and associated fractures than black women. Other risk factors, such as smoking and lack of exercise, also contribute to the development of osteoporosis, but they are not strong risk factors. In general, the more risk factors a woman has, the higher the likelihood that she has or will develop osteoporosis. However, some risk factors, such as chronic use of high-dose corticosteroids, are sufficiently strong that even in isolation they signal the need for further evaluation, including BMD testing.

**Concern About Osteoporosis**

Many women present without specific risk factors for osteoporosis but are concerned that they may have osteoporosis or
be at risk for developing it. The absence of risk factors does not mean that a woman’s BMD is normal or that a fracture will not occur. Therefore, if available, BMD testing should be offered to these patients.

DIFFERENTIAL DIAGNOSIS AND INVESTIGATION

Differential Diagnosis

Malignancies with skeletal metastases and multiple myeloma may cause vertebral fracture or, less commonly, fracture at other sites. The diagnosis is usually suggested by the severity of the pain or the general physical findings and is confirmed by laboratory tests, roentgenograms, or bone scintigraphy. In some cases, the diagnosis may be more difficult to confirm, necessitating a computed tomography scan, magnetic resonance imaging, or histologic examination of a bone specimen.

Osteomalacia can mimic osteoporosis and induce biconcavity of several vertebrae. The defect of mineralization of bone matrix is usually a result of impaired intake, production, or metabolism of vitamin D, although less commonly it may be due to intestinal malabsorption or impaired phosphate transport. The diagnosis is usually suggested by the clinical history and by abnormalities on biologic tests, as by low serum and urinary calcium, high serum alkaline phosphatase, and low serum 25-hydroxyvitamin D in the case of vitamin D deficiency. If the diagnosis is uncertain, a transiliac bone biopsy may be necessary.

Other spinal disorders can produce vertebral deformities that may mimic vertebral fracture on roentgenograms, including osteoarthrosis, severe scoliosis, and long-term sequelae of Scheuermann’s disease.

Investigation

The clinical history, physical examination, and laboratory tests are directed at excluding a disease that resembles osteoporosis, identifying contributory factors that may require specific interventions, and assessing the severity of confirmed osteoporosis (ie, the magnitude of fracture risk). The following diagnostic procedures fulfill these requirements.

Routine Procedures

The physical examination should include measurement of height (using a stadiometer, if possible) to detect height loss. In addition to the history and physical examination, the following laboratory measurements are obtained routinely: a complete blood cell count; erythrocyte sedimentation rate; and levels of serum calcium, phosphate, alkaline phosphatase, creatinine, and albumin. Lateral roentgenograms of the lumbar and thoracic spine are obtained to document or exclude the presence of vertebral fracture (particularly in patients aged >65 years with kyphosis or height loss) and to exclude other skeletal pathology (eg, metastatic bone disease). BMD measurements include dual-energy x-ray absorptiometry (DXA) of the spine and hip; single energy x-ray absorptiometry or DXA of the forearm or heel if spine/hip DXA is not available; and heel ultrasound or another validated technique if none of the above are available. Analysis of serum or urine markers of bone turnover are not required but are helpful in assessing the rate of bone turnover and in monitoring the response to treatment with inhibitors of bone turnover.46,52

The availability of the technology for measuring BMD is improving, although access remains limited in some practice settings. Where available, BMD measure-
ment should be performed in patients with recent fracture, as well as in those with risk factors for osteoporosis. Risk factors include prolonged amenorrhea during the reproductive years, early menopause (before age 45), current age of ≥65 years, thin build, maternal history of hip fracture, use of corticosteroids (including inhaled forms, particularly if equivalent to ≥7.5 mg/d prednisone) for ≥6 months, any fracture after age 45 (particularly of the hip, vertebra, wrist/forearm, humerus, rib, or pelvis), or the presence of any disease or condition known to predispose to osteoporosis (eg, malabsorption, hyperparathyroidism, hyperthyroidism, chronic inflammatory diseases, alcoholism, and prolonged immobilization in bed or wheelchair).

DXA of the spine is useful in women aged <65 years, but in older women osteoarthritis of the lumbar spine often results in overestimation of lumbar spine BMD. The hip is generally a preferred site for BMD measurement, because the BMD of the hip is the best predictor of hip fracture. However, for assessing the risk of fracture in general, measurement of more peripheral sites, such as the heel or distal radius, are as useful as measurement of the spine or hip. Average T-scores for specific age groups may differ by measurement site and technique used, but there is some evidence suggesting that these differences may not impair the ability to diagnose osteoporosis and low bone mass. Thus BMD measurement at any site is of value in making the diagnosis of osteoporosis.

Identification of Contributory Factors and Assessment of Prognosis

It is necessary to identify the presence of various factors and disorders that are associated with an increased risk for osteoporosis, since they may require specific interventions. These include inactivity, smoking, excessive alcohol intake, medical disorders (eg, primary hyperparathyroidism, thyrotoxicosis, gastrointestinal malabsorption, rheumatoid arthritis, chronic obstructive lung disease), and use of particular drugs (especially chronic corticosteroid therapy, but also use of anticonvulsant agents, drugs that induce hypogonadism, and excessively high levels of thyroid hormone replacement therapy).

Assessment of the prognosis of osteoporosis may be valuable for making treatment decisions. The severity of osteoporosis (ie, the magnitude of the risk for subsequent vertebral and peripheral fractures) is established mainly by (1) the BMD (ie, the lower the BMD, the higher the risk of fracture—fracture risk approximately doubles with each 1-SD decrease in BMD); (2) a history of previous fractures (number of vertebral fractures, history of appendicular fractures) or a maternal history of hip fracture; (3) an increased rate of bone turnover, as assessed by biochemical markers (increased bone turnover is an independent risk factor for vertebral and hip fracture); and (4) the presence of risk factors not captured by BMD measurement, including frailty, advanced age, and increased risk of falling.

For simplicity, the current definition of osteoporosis focuses exclusively on current BMD. Thus a patient whose current T-score falls below −2.5 is considered to have osteoporosis. One whose T-score is between −1 and −2.5 has "low bone mass,"

Additional Laboratory Investigations

The clinical circumstances should guide the use of the additional investigations listed in Table I to exclude or confirm specific diagnoses of disorders having effects on bone.
Table I. Additional laboratory investigations for osteoporosis.

<table>
<thead>
<tr>
<th>Test</th>
<th>Clinical Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum and urine markers of bone turnover</td>
<td>Assess bone turnover</td>
</tr>
<tr>
<td></td>
<td>Monitor antiresorptive therapy</td>
</tr>
<tr>
<td>Serum PTH</td>
<td>Hypercalcemia</td>
</tr>
<tr>
<td>25-hydroxyvitamin D, 24-hour urinary calcium</td>
<td>Possible vitamin D insufficiency</td>
</tr>
<tr>
<td>TSH, free T₄</td>
<td>Possible hyperthyroidism</td>
</tr>
<tr>
<td>24-Hour urinary free cortisol or fasting serum cortisol</td>
<td>Possible Cushing’s disease/syndrome</td>
</tr>
<tr>
<td>Serum protein electrophoresis, serum and urine immunoelectrophoresis, cancer markers, bone marrow examination</td>
<td>Possible malignancy, particularly in patients with vertebral fracture</td>
</tr>
<tr>
<td>Transiliac bone biopsy after tetracycline double labeling for histomorphometry</td>
<td>Possible osteomalacia</td>
</tr>
</tbody>
</table>

PTH = parathyroid hormone; TSH = thyroid-stimulating hormone; T₄ = thyroxine.

and patients with T-scores above this range have normal bone mass.43 However, these diagnostic thresholds should not be applied rigidly to determine the appropriateness of treatment for an individual. Physicians should consider the probability that a particular patient will develop fractures during her lifetime as a result of other factors combined with BMD. For example, a woman who has had a vertebral fracture has approximately 4 times the risk of having another vertebral fracture and twice the risk of hip fracture compared with a woman of the same age and BMD who has not had a fracture; therefore, she should be treated even if her current T-score is above −2.5.10,12,13,55,56 A 42-year-old woman who has just undergone menopause and has a T-score of −1.5 is at increased risk for osteoporosis and fractures in later life and would be a good candidate for treatment to prevent bone loss. However, a T-score of −2.6 in a 90-year-old woman with no history of fracture or other risk factors may not require specific intervention, since her remaining lifetime risk of fracture is likely to be low. There are tools for evaluating the remaining lifetime risk of fracture that may be useful to both physicians and patients when considering the need for treatment.57

MANAGEMENT

General Measures

The treatment of acute back pain due to a recent vertebral fracture includes bed rest (as short as possible), back support, analgesic agents/nonsteroidal anti-inflammatory drugs (NSAIDs), heat, and gentle...
massage. The treatment of chronic back pain due to vertebral fracture is difficult but includes analgesic agents/NSAIDs, physiotherapy, intermittent use of spinal support for some activities, and a program of physical activity to maintain muscle strength and flexibility of the spine.58

In all patients, it is important to treat diseases that can increase bone loss and contribute to osteoporosis. An important part of the management of patients with osteoporosis—particularly those who have had a hip fracture and otherwise frail patients—is attending to their general health status (eg, ensuring adequate protein intake) and suggesting measures to decrease their risk of falls or the degree of trauma resulting from falls (eg, installation of carpeting, better lighting, or handrails; removal of obstacles; attention to use of such drugs as sedative, narcotic analgesic, anticholinergic, and antihypertensive agents that may predispose the patient to falls; and use of hip padding).59

Regular exercise may be of value in maintaining mobility and improving muscle mass, thus reducing patients' risk of falling. Patients with osteoporosis should avoid heavy weight-bearing and vigorous exercise programs, because such activity may trigger a new fracture.

Calcium and Vitamin D

Low calcium intake and vitamin D deficiency should be remedied in all patients. Because many hip fractures occur in patients aged ≥80 years and this population is particularly prone to low calcium intake and vitamin D deficiency, it is important to ensure that these patients receive adequate calcium and vitamin D as part of their management. In patients who habitually consume little calcium, the use of calcium alone has been reported to induce small increases in spine BMD and a possible decrease in the incidence of fractures.60-62 However, the use of low-dose vitamin D (400 IU/d) alone did not reduce fracture incidence in a free-living, ambulatory population of Dutch postmenopausal women.63 In contrast, in a French study of women in nursing homes, many of whom had insufficient vitamin D intake, the use of calcium and vitamin D (800 IU/d) together decreased the incidence of hip fractures.64,65

These data underscore the importance of ensuring that all postmenopausal women receive adequate calcium and vitamin D. Ambulatory patients exposed to sunlight for >15 minutes a day generally produce sufficient vitamin D through skin photoconversion, but others should receive a supplement containing 400 to 800 IU/d of vitamin D. Total daily intake of calcium, including supplements if necessary, should be at least 1000 mg. Despite the necessity of adequate calcium and vitamin D for bone health, treatment with calcium and vitamin D alone is insufficient to prevent postmenopausal bone loss or to reduce fracture risk markedly in patients with osteoporosis.

Pharmacologic Intervention

As with all therapeutic decisions, physicians should consider the benefits, risks, and costs of each pharmacologic treatment as it applies to the individual patient and should refer to current package inserts for complete details of a drug's indications and use.66

Whenever possible, our advice concerning the selection of pharmacologic therapy has been based on the scientific evidence from randomized clinical trials that include a prospectively defined fracture end point.67
The prospective controlled data strongly support the efficacy of alendronate in preventing vertebral and nonvertebral fractures (including hip fracture). The prospective controlled data strongly support the efficacy of alendronate in preventing vertebral and nonvertebral fractures (including hip fracture). Several observational studies have indicated that estrogen use is also associated with a substantial reduction in fracture risk. The strength of the data from randomized, controlled trials concerning vertebral and hip fracture are summarized in Table II. In most of the clinical trials, all patients were given adequate calcium and vitamin D; thus in these studies antifracture efficacy reflects a decrease in fracture incidence beyond that achievable with calcium and vitamin D alone.

**Estrogen**

Considerations associated with the decision to initiate estrogen therapy include its potential benefits (eg, relief from the symptoms of estrogen deficiency [hot flashes] and cardioprotection) and its risks (eg, increased risk of breast and endometrial cancer). Concomitant use of estrogen with a progestin (hormone replacement therapy [HRT]) in women with an intact uterus minimizes the increased risk of endometrial cancer. Estrogen use increases the risk of venous thromboembolic events by 2 or 3 times. Some women cannot tolerate estrogen or HRT, although side effects can sometimes be alleviated by changing the treatment regimen. In older postmenopausal women, it is important to begin therapy at a low dose that is increased over several months.

The long-term clinical data on estrogen use are derived principally from observational studies. There are no published fracture data (as of November 1998) on risedronate or raloxifene. Studies are in progress, as is a new study of calcitonin, and data are likely to be published in the near future.

**Table II. Evidence of antifracture efficacy from randomized clinical trials.**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Reference</th>
<th>Evidence for Reduction of Vertebral Fracture Risk</th>
<th>Evidence for Reduction of Nonvertebral Fracture Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>68–71</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Estrogen</td>
<td>76</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Etidronate</td>
<td>77–79</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Risedronate†</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Raloxifene†</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intranasal calcitonin</td>
<td>80</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Fluoride salts</td>
<td>81–83</td>
<td>±</td>
<td>–</td>
</tr>
<tr>
<td>Vitamin D analogues</td>
<td>84,85</td>
<td>±</td>
<td>0</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tibolone</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ipriflavone</td>
<td>None</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

++ = strong evidence for antifracture efficacy; + = some evidence for antifracture efficacy; 0 = insufficient evidence for antifracture efficacy; ± = variable or equivocal effects reported; − = increased fracture risk reported.

*In the majority of these studies, the control group received calcium supplements and adequate vitamin D. Thus the effects noted are in excess of those produced by calcium and vitamin D alone.

†Substantial evidence for antifracture efficacy of estrogen is available from several observational studies. There are no published fracture data (as of November 1998) on risedronate or raloxifene. Studies are in progress, as is a new study of calcitonin, and data are likely to be published in the near future.
tional studies, with relatively few data available from randomized, controlled studies. At adequate doses, estrogen maintains or increases bone mass, including increases of 2% to 8% in spine and hip BMD. Although women who take estrogen have fewer fractures than those who do not, previous users of estrogen do not appear to have any significant residual reduction in fracture risk compared with women who never take estrogen after menopause. Therefore, to reduce lifetime fracture risk significantly, a woman must continue taking estrogen. However, most postmenopausal use of estrogen is directed at treating climacteric symptoms, and once these subside the majority of women discontinue estrogen use.

Alendronate

Data are available from several large, randomized, controlled clinical trials of up to 5 years’ duration in patients with osteoporosis or low BMD treated with alendronate. These studies demonstrate that alendronate increases bone density by 5% to 10% at the spine and hip and decreases the risk of fracture at these sites by about 50%. Other studies of alendronate have shown prevention of bone loss in early postmenopausal women. In these studies, bone density increased by 3% to 5% at the spine and hip compared with placebo. Some patients taking alendronate developed esophagitis or esophageal ulcer, which was often associated with improper administration. In some patients, upper gastrointestinal (GI) symptoms may lead to discontinuation of treatment. However, in many cases the relationship between alendronate use and upper GI symptoms is unclear. Bone loss resumes once a patient stops taking alendronate, but this is not accelerated compared with placebo. Thus previous gains in BMD are maintained, but continued therapy is required to obtain progressive increases in BMD.

Cyclic Etidronate

Data are available from 2 randomized, controlled trials of up to 3 years’ duration in patients with osteoporosis treated with cyclic etidronate. In these studies, cyclic etidronate increased bone density by 1% to 5% at the spine and hip, and, in post hoc analyses of a subset of patients, the incidence of spine fractures decreased. However, this decrease was not significant when all patients were included in the analyses. Some patients from these trials have been treated for up to 7 years. Etidronate has also been reported to prevent bone loss in early postmenopausal women. Some cases of impaired mineralization of bone have been reported with cyclic etidronate.

Raloxifene

Published data are available from a 2-year, randomized, controlled clinical trial of raloxifene in early postmenopausal women. Bone density increased by 2% at the spine and hip compared with placebo. Low-density lipoprotein cholesterol levels decreased by 10%, but no effects were observed on levels of high-density lipoprotein cholesterol. The effects on cardiovascular end points have not been reported. Hot flashes and muscle cramps occurred at a higher incidence in patients taking raloxifene than in those taking placebo. Like estrogen, raloxifene is associated with a twofold to threefold increase in the risk of venous thromboembolic events. However, unlike estrogen, raloxifene does not stimulate the endometrium.
Intranasal Calcitonin

In a small, controlled, 2-year dose-finding study of intranasal calcitonin in postmenopausal women with osteoporosis, spine BMD increased by 2%.80 There was no effect on other skeletal sites. A lower incidence of vertebral fractures was noted compared with placebo.

Other Treatments

Other treatments for osteoporosis include fluoride salts, various vitamin D analogues, anabolic steroids, tibolone, and ipriflavone. These agents are available in some countries but not others, and evidence for their antifracture efficacy varies markedly and is less strong than the evidence for estrogen and alendronate (Table II).

Fluoride salts have been reported to increase spine BMD substantially.81 Despite this, vertebral fracture rates have not been shown to decrease in adequate controlled trials.81,82 In addition, fluoride induces a dose-dependent increase in stress fracture and possibly in hip fracture. For these reasons, fluoride salts should not be used in routine clinical practice.

Calcitriol (1,25(OH)₂vitamin D₃) and other analogues of vitamin D have variable effects on BMD, showing no change, increases of 1% to 2%, or decreases compared with placebo.85 Potential side effects include hypercalcemia and hypercalciuria. These agents have not demonstrated consistent antifracture efficacy in masked, placebo-controlled studies.84,103,104

No fracture end point studies have been conducted for anabolic steroids, tibolone, or ipriflavone.

FOLLOW-UP

Once patients have been identified and treatment initiated, it is important to arrange adequate follow-up to reinforce the importance of compliance with treatment and to evaluate the response. At minimum, all treated patients should be seen after 3 to 6 months of treatment and thereafter at least annually. The importance of adherence to treatment should be stressed. The regimen of estrogen (with or without added progestin) may require adjustment to patients' needs.

The response to therapy can be monitored using tests of biochemical markers or repeat BMD measurement and may be of value in assessing compliance and providing patient feedback. Although optional, it is possible to assess the response to such antiresorptive treatments as estrogen or alendronate after 3 to 6 months by assessing the change in biochemical markers of bone turnover, such as N-terminal or C-terminal crosslinks of type I collagen, serum osteocalcin, or serum bone-specific alkaline phosphatase. In most patients, these markers decrease by >30% compared with baseline (ie, pretreatment) or are reduced to within the premenopausal reference range, evidence that treatment is having the desired effect of decreasing bone turnover. Changes in BMD occur over a longer period, and it is generally not useful to repeat BMD measurement until completion of 1 or 2 years of therapy and every 2 years thereafter. The majority of patients receiving efficacious therapy will have a measurable increase in BMD at the spine and hip (especially at the trochanter subregion) after 2 years of treatment. The typically small increases in BMD at peripheral sites, such as the heel and forearm, relative to the precision of the measurements make these sites unreliable for the purposes of assessing the response to treatment.
Development of these guidelines was supported by an educational grant from Merck & Co., Inc., Whitehouse Station, New Jersey. The opinions expressed represent the consensus of the committee members and are independent of the sponsor.

Address correspondence to: Pierre J. Meunier, MD, Professor of Medicine, Hôpital Edouard Herriot—Pavillon F, Place d’Arsonval, 69437 Lyon cedex 03, France.

REFERENCES


