CASE-BASED REVIEW

Diagnosis and Management of Postmenopausal Osteoporosis

Case Study and Commentary, Bart L. Clarke, MD

INSTRUCTIONS

The following article, “Diagnosis and Management of Postmenopausal Osteoporosis,” is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation form on page 408.

OBJECTIVES

After participating in the continuing education activity, primary care physicians should be able to:
1. Appreciate the value of measuring bone mineral density in patients with osteoporosis
2. Identify risk factors for postmenopausal osteoporosis
3. Know common secondary causes of osteoporosis and recognize the importance of evaluating patients to rule out these causes
4. Know available pharmacologic and nonpharmacologic interventions for prevention and treatment of osteoporosis
5. Be familiar with laboratory tests for monitoring patients’ response to treatment

It is currently estimated that 28 million Americans have low bone density, with approximately 10 million of these individuals meeting current World Health Organization criteria for osteoporosis and 18 million meeting the criteria for osteopenia [1]. The prevalence of osteoporosis in the United States is estimated to range from 12% to 15%, depending on the state, with the highest prevalence estimates in upper central Midwest states [2]. The average 50-year-old white woman in the United States has a 40% risk of a clinical fracture in her remaining lifetime years, but this increases to roughly 50% if radiograph-documented asymptomatic vertebral fractures are included in the risk estimate [3]. It is evident that osteoporosis is a U.S. public health problem. However, osteoporosis tends to be overlooked because it is usually not recognized until fractures occur, and because many patients and some physicians consider it to be a normal part of the aging process. Physicians who would otherwise treat osteoporosis may not do so because they are preoccupied with addressing more pressing medical problems faced by their patients.

Patients who do not pay attention to their osteoporosis until fractures occur are often surprised by the severity of the consequences of their fractures. This is especially true for patients with hip fractures, who experience a 20% increased mortality in the first year after hip fracture than would otherwise be expected for age, often due to coexisting illnesses or deep venous thrombosis and pulmonary embolism that result from the relative immobilization associated with hip fracture [4]. Most patients who survive hip fracture are significantly limited in their ability to carry out activities of daily living, and many require prolonged institutional care and/or help at home afterward. Patients with wrist, vertebral, or other osteoporotic fractures experience pain and temporary disability, usually with less severe functional consequences than after hip fracture. Those with single or multiple vertebral compression fractures often experience chronic back pain, loss of height, kyphosis, abdominal protruberance, and loss of self-esteem. The cost of caring for patients with osteoporotic fractures in the United States in 1995 was estimated to be $14.6 billion [5].

Patients with osteoporotic fractures should automatically be considered for measurement of bone mineral density (BMD) and screening for secondary causes of bone loss. However, physicians may fail to act on BMD information when it is obtained, and they often do not evaluate for secondary causes of bone loss in postmenopausal women. Studies suggest that 11% to 31% of postmenopausal women have an identifiable factor or factors contributing to bone loss beyond postmenopausal status that can be modified or treated [6,7]. Physicians may treat patients with antiresorptive medication for osteoporosis without measuring BMD or looking for secondary causes in the belief that additional knowledge about severity of bone loss or factors contributing to bone loss would not influence treatment decisions.

From the Division of Endocrinology, Metabolism, Diabetes, and Nutrition, Mayo Clinic, Rochester, MN.
CASE STUDY
Initial Presentation
A 65-year-old white woman presents to her primary care physician for evaluation of acute onset of severe pain in her mid and low back that began 2 days ago while she was gardening.

History
The patient reports that she has been healthy for her entire life. Two days ago, she knelt down and bent forward to plant a new rose bush. She felt immediate onset of severe mid and low back pain over her spine, without radiation. Spine radiographs obtained at her local emergency department shortly thereafter confirmed the presence of T11 and T12 vertebral compression fractures and an L2 superior endplate fracture. She was given an injection of nonsteroidal pain medication and sent home with prescriptions for oral narcotic and nonsteroidal pain medications for use as needed. Her pain is still moderately severe but is gradually improving.

The patient previously took postmenopausal hormone replacement therapy following spontaneous menopause at age 52 years but discontinued it after 2 years due to persistent breast tenderness and nausea. She has not taken other osteoporosis medications in the past. She has not ever been diagnosed with osteoporosis and has not had a BMD test. Her previous calcium intake has been excellent, and she claims to have drunk at least 3 glasses of milk every day for her entire adult life, in addition to taking a calcium supplement in the form of calcium citrate 600 mg daily for most of the last 10 years. She thinks she may have lost about 1 1/2 inches in height over the last 10 years.

The patient has had essential hypertension for about 5 years, which is treated currently with triamterene/hydrochlorothiazide 37.5/25 mg daily and lisinopril 10 mg daily. She was diagnosed with seronegative inflammatory polyarthritis about 8 years ago and has taken prednisone 10 mg daily and methotrexate 12.5 mg per week since then. She previously smoked a half pack of cigarettes per day for 20 years, but quit 10 years ago. She has drunk a glass of wine with dinner each day for many years. She has had a cup of coffee each day for most of the past 30 years.

Family history is significant for recurrent calcium-containing kidney stones in one brother, and postmenopausal osteoporosis in her older sister diagnosed at age 68 years after a Colles’ fracture. She denies any other family history of metabolic bone disease.

Physical Examination
The patient’s height is 5’ 2”, weight is 120 lb, and blood pressure is 146/86 mm Hg in the left arm while sitting. Pulse is regular at 78 bpm. Physical examination is significant for mild synovitis of the metacarpophalangeal joints and moderate thoracic kyphosis with palpation tenderness over the T11 and T12 vertebral area.

Laboratory Evaluation
Laboratory studies show a mildly increased serum calcium of 10.3 mg/dL (normal, 8.9–10.1) and normal serum phosphorus, total alkaline phosphatase, creatinine, complete blood count, erythrocyte sedimentation rate, aspartate transaminase (AST), serum protein electrophoresis, and sensitive thyroid-stimulating hormone (TSH). Twenty-four-hour urinary calcium is 180 mg (normal, 20–275). A lateral chest radiograph taken 8 months ago because of persistent dry cough showed no vertebral compression or wedge fractures, although ballooning of the interspaces was noted at several thoracic levels.

• Should a patient with evident postmenopausal osteoporosis and documented vertebral compression fractures have a bone density test?

Measurement of BMD
Postmenopausal osteoporosis is a systemic skeletal disease associated with decreased BMD and microarchitectural deterioration of bone, which results in an increased risk of atraumatic or nontraumatic fractures [8]. While by this definition a fracture is not required in order to diagnose osteoporosis, occasional patients develop fractures not due to osteoporosis. The assumption that all nontraumatic fractures are due to osteoporosis is incorrect. If a patient with an apparent nontraumatic fracture has normal BMD or only mild osteopenia, pathological causes of fracture such osteomyelitis, metastasis, or other bone abnormality should be considered.

The BMD test offers information beyond simple quantitative assessment of bone density. The Z score, commonly reported with the T score, may be helpful in determining which patients require more extensive evaluation for secondary causes of osteoporosis. Patients who meet current diagnostic criteria for osteoporosis may do so simply because of advanced age or because of other factors. If the patient’s Z score, which compares patients’ BMD to the mean BMD of their peer group of age-, ethnicity-, and sex-matched individuals, is significantly reduced, secondary causes of bone loss may be present. Of course, patients with markedly decreased T scores should also be considered for possible secondary causes of bone loss, based on the magnitude of the severity of their bone loss (Table 1). The T score compares the patient’s BMD to the mean of young adult ethnicity- and sex-matched controls who are at peak bone density.

BMD is typically measured at the lumbar spine and non-dominant hip by central dual-energy X-ray absorptiometry.
Bone Densitometry and Diagnosis

Because the patient has not previously had a BMD test and because she is reluctant to consider antiresorptive osteoporosis medication due to cost, a DEXA test of the lumbar spine and nondominant hip is ordered to assess the severity of her osteoporosis. Lumbar spine BMD is 0.700 g/cm² (T score –4.1, Z score –2.6), and left femoral neck BMD is 0.660 g/cm² (T score –2.6, Z score –0.7). These measurements are diagnostic of significant osteoporosis at the lumbar spine and mild osteoporosis at the left hip.

She is diagnosed with significant postmenopausal osteoporosis as the cause of her T11 and T12 vertebral compression fractures and L2 superior endplate collapse fracture, based on the workup and emergency room radiographs. The diagnosis is complicated by chronic glucocorticoid dependence and mild hypercalcemia of uncertain origin. No other secondary causes for her bone loss are identified.

- What is the time course of acquisition and loss of BMD?

Postmenopausal osteoporosis results from the summation of various processes causing bone loss in an individual patient. Excessive loss of BMD in early postmenopausal years may be due predominantly to the effects of estrogen deficiency. BMD typically is acquired rapidly at puberty due to onset of gonadal steroid secretion. Acquisition of skeletal mineral continues through the late second and third decades in most individuals, with peak BMD achieved in the late third to early fourth decade in most patients. Age-related bone loss is thought to begin slowly in the latter part of the fourth decade, long before menopause begins. The specific causes of premenopausal age-related bone loss are not yet known. Women lose bone density rapidly during and early after menopause, but bone loss may begin before the patient is even aware she is entering menopause. Early postmenopausal rapid bone loss appears to continue for 10 to 15 years, if not prevented, and is attributed primarily to estrogen deficiency. After rapid early postmenopausal bone loss, women continue to lose BMD more slowly for the remainder of their lives. Late postmenopausal bone loss is thought to be due to several factors, including physiological hyperparathyroidism, subclinical vitamin D deficiency, increased local or systemic secretion of bone-resorbing cytokines, and other factors [14].

- What are the risk factors associated with postmenopausal osteoporosis?

Risk Factors

Epidemiologic studies have identified a number of risk factors for osteoporosis, each of which adds a small relative risk [15–18]. Postmenopausal status, nulliparity, late age of onset of menarche, or early age of menopause increase risk of osteoporosis. Eating disorders such as anorexia nervosa, exercise-induced hypothalamic amenorrhea, or any cause of oligomenorrhea or amenorrhea during childbearing years increase the risk of osteoporosis. Genetic inheritance is estimated to cause 60% to 70% of the variance in bone density, which explains why women of northern European and southeast Asian descent are at particular risk for osteoporosis. Regardless of ethnicity, a family history of osteoporosis should suggest increased risk of osteoporosis. Slender body habitus and adult body weight of less than 127 lb have been identified as risk factors. Environmental factors are thought responsible for 30% to 40% of variance in bone density. Excess alcohol intake, malnutrition, tobacco use, and lack of physical exercise are risk factors, as are dietary habits such as low calcium or vitamin D intake and high sodium, high protein, or high caffeine intake. Environmental factors may be modifiable in many patients.
Many postmenopausal women consume less than the recommended daily amounts of calcium or vitamin D [19]. However, calcium intake in American women has gradually improved over the past 2 decades, based on data from sequential National Health and Nutrition Examination Surveys. Both dietary and supplemental calcium are effective at preventing postmenopausal bone loss.

Several risk factors for fracture have also been reported. Family history of osteoporotic fracture, personal history of fracture, propensity to fall, and use of medications predisposing to falls all influence a patient’s risk of osteoporotic fracture. Medications that might predispose to falls include opiates, benzodiazepines, antipsychotics, and antihypertensives, which might increase dizziness, imbalance, and lack of coordination and judgment or decrease blood pressure, thereby leading to increased risk of falling. Some of these factors may be modifiable.

• What is the differential diagnosis of secondary causes of osteoporosis in this patient?
• What tests are used to assess for secondary causes?

Patients with severe bone loss or bone loss disproportionate to that expected for age should be considered as possibly having secondary causes of bone loss. In addition, patients with recognized diseases or conditions known to cause bone loss should be considered to have secondary causes of their osteoporosis. The major challenge is to identify those patients who appear to be otherwise healthy but have unrecognized secondary causes of bone loss. Given that as many as half of men with osteoporosis and between 11% and 31% of women with postmenopausal osteoporosis have at least one identifiable factor contributing to their osteoporosis [6,7], secondary causes should be considered in the evaluation of every patient with osteoporosis. The case patient has required glucocorticoid therapy for several years due to inflammatory polyarthritis, and also has documented mildly increased serum calcium of unclear origin. Of course, further testing might reveal other abnormalities that could be contributing factors. The differential diagnosis of secondary causes of postmenopausal osteoporosis is shown in Table 2.

Patients diagnosed with postmenopausal osteoporosis should undergo screening studies to rule out common secondary causes of osteoporosis. Serum total calcium, phosphorus, total alkaline phosphatase, creatinine, AST, sensitive TSH, erythrocyte sedimentation rate, and serum protein electrophoresis should be measured if they have not been assessed in the preceding 6 months. These tests will rule out relatively common disorders of bone and calcium metabolism that cause bone loss, such as primary and secondary hyperparathyroidism, as well as other disorders known to cause bone loss, such as primary biliary cirrhosis and other liver diseases, hyperthyroidism, and multiple myeloma and other monoclonal disorders. Appropriate spine radiographs should be checked to evaluate for fractures, especially if asymptomatic vertebral fractures may be present. Spine radiographs are important to document fractures, because not all patients with kyphosis have vertebral fractures.

Clinical judgment should be used in deciding whether further tests are necessary. Twenty-four hour urinary calcium and creatinine measurement will detect hypercalcuria in patients without a history of calcium-containing kidney stones, which may be due to a renal calcium leak, increased intestinal absorption of calcium, or excessive loss of bone calcium. Patients with low 24-hour urinary calcium (less than 100 mg) may have unrecognized inadequate calcium or vitamin D intake or malabsorption.

• What secondary causes of osteoporosis are suggested by the patient’s laboratory test results?
• Should therapy be initiated at this point?

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**Table 2. Common Secondary Causes of Osteoporosis**

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disease</td>
<td>Cushing’s syndrome, Hypogonadism of any cause, Hyperthyroidism, Hyperparathyroidism, Type 1 diabetes mellitus</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Multiple myeloma, Leukemia, Systemic mastocytosis</td>
</tr>
<tr>
<td>Drugs</td>
<td>Glucocorticoids, Levothyroxine overreplacement, Anticonvulsants: phenytoin or phenobarbital</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>methotrexate or other antimetabolites</td>
</tr>
<tr>
<td>Chronic obstructive liver disease: primary biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>of any type leading to malabsorption or malnutrition</td>
</tr>
<tr>
<td>Immobilization</td>
<td>spinal cord syndromes, prolonged bed rest</td>
</tr>
<tr>
<td>Genetic diseases</td>
<td>osteogenesis imperfect</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>alcohol abuse, anorexia nervosa, Parkinson’s disease</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>idiopathic osteoporosis of young adults, regional osteoparosises associated with reflex sympathetic dystrophy</td>
</tr>
</tbody>
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**POSTMENOPAUSAL OSTEOPOROSIS**
This patient had a mildly increased serum calcium and normal serum phosphorus level, with a mid-normal 24-hour urinary calcium while taking a thiazide diuretic. The patient could have mild primary hyperparathyroidism with a mid-normal 24-hour urinary calcium due to thiazide-related decreased urinary calcium excretion, or her mild hypercalcemia might be due to a side effect of the thiazide diuretic. It is unlikely the patient is taking too much calcium or vitamin D in her diet to cause mild hypercalcemia, since typically serum calcium and phosphorus are both mildly increased in this situation. Chronic glucocorticoid therapy typically reduces intestinal calcium absorption and increases urinary calcium excretion.

Starting treatment for the patient’s osteoporosis before knowing the results of further workup to evaluate for the conditions discussed above may affect a number of the results that would alter subsequent treatment recommendations. For example, oral bisphosphonate therapy may decrease 24-hour urinary calcium, which might then affect decisions about what to do should primary hyperparathyroidism be present. Of course, it is important to begin treatment for osteoporosis as soon as it is reasonable to do so.

Further Laboratory Evaluation and Initial Management

To sort out the cause of her abnormalities, the patient is advised to stop her thiazide diuretic for 1 month and undergo laboratory evaluation on the lowest dose of glucocorticoid she will tolerate. After her hydrochlorothiazide is stopped for 1 month, repeat serum calcium is 10.5 mg/dL and phosphorus is 2.8 mg/dL. Repeat 24-hour urinary calcium is increased at 380 mg. Whole-molecule parathyroid hormone level is increased at 7.5 pmol/L (normal, 1.0–5.2). Serum creatinine remains normal, and serum 25-hydroxyvitamin D is normal at 25 ng/dL (normal, 8–38). In light of these findings, the patient is diagnosed with primary hyperparathyroidism. Radiograph of the kidneys, ureters, and bladder shows no evidence of calcium-containing kidney stones. Parathyroid sestamibi scan shows uptake in the right tracheoesophageal groove, consistent with a parathyroid adenoma, and she is referred for minimally invasive surgery. A 280-mg right upper parathyroid adenoma is removed. Her postoperative serum calcium and phosphorus normalize within 6 hours of surgery.

• How should the patient’s osteoporosis be treated after surgical cure of her primary hyperparathyroidism?

After cure of her primary hyperparathyroidism, it is likely the patient’s BMD will improve to some degree without further therapy. However, she has severe osteoporosis with a history of spontaneous fractures, and it would be prudent to treat her with an antiresorptive agent. The primary hyperparathyroidism was mild, and cure of this may not be sufficient, by itself, to significantly improve her BMD.

Exercise and Nutritional Supplements

All patients with postmenopausal osteoporosis should attempt weight-bearing exercise by walking for a minimum of 3 hours per week. This level of activity may improve lumbar spine and hip bone mineral density by 1% to 3% in younger women [20–23], and also may improve balance, coordination, sense of well-being, and fall risk. No study has demonstrated that exercise reduces fracture risk in any population studied. Strength training maintained BMD at the lumbar spine but not at other skeletal sites in early postmenopausal women [24]; brisk walking did not maintain or protect against bone loss in older women in one study [25]. Several studies have shown that resistance exercise or mixed resistance/endurance exercise increased bone density in older men and women [26–28], whereas another study showed that exercise prevented bone loss in postmenopausal women [29].

Adequate calcium intake may help prevent fractures [30–38]. The 1994 National Institutes of Health Consensus Conference recommended that calcium intake by postmenopausal patients with osteoporosis should be 1500 mg per day if they are not taking estrogen [39]. The daily amount recommended by the 1997 National Academy of Sciences for healthy postmenopausal individuals is slightly less [40].

Vitamin D supplementation will stimulate calcium and phosphorus absorption from the small intestine. This is important because intestinal calcium absorption decreases with age, due in part to decreased synthesis of serum 1,25-dihydroxyvitamin D by declining renal 1α-hydroxylase activity, and to decreased intestinal responsiveness to serum 1,25-dihydroxyvitamin D. Many older adults in northern latitudes have subnormal levels of the body storage form of vitamin D, serum 25-hydroxyvitamin D [41]. Vitamin D supplementation has been shown to reduce fractures in the elderly [42,43]. Vitamin D supplementation of 400 IU/day in the form of 1 multivitamin per day is often adequate to obtain at least mid-normal serum 25-dihydroxyvitamin D levels in most postmenopausal women until age 70 years, after which higher doses may be required. However, the case patient is still taking prednisone 10 mg per day. Patients taking prednisone 10 mg/day or more should be given vitamin D 800 IU per day to help compensate for glucocorticoid-induced decreased intestinal calcium absorption and increased renal calcium excretion [44].

Pharmacotherapy

A variety of agents are approved for prevention and treatment of postmenopausal osteoporosis (Table 3). The choice of agent...
often depends on the severity of postmenopausal bone loss and side effects of the agents available. In many cases the agent chosen will be the most potent drug the patient can tolerate.

### Estrogen/Hormone Replacement Therapy

Estrogen or hormone replacement remains an option in a patient without contraindications but may be less effective for prevention of bone loss than once thought. It is now approved only for prevention, but not treatment, of osteoporosis. Postmenopausal estrogen deficiency results in increased production of several interleukins, tumor necrosis factor-α, and granulocyte-macrophage colony stimulating factor, and decreased production of transforming growth factor-β by bone cells [45], as well as decreased intestinal calcium absorption and increased renal calcium excretion. Two small randomized controlled trials showed a small prospective benefit of estrogen or hormone replacement therapy on improved BMD or fracture reduction [46,47], as have many observational studies over the past 20 years [48–52]. The major concern with estrogen replacement is the risk of reproductive tissue malignancy [53]. It is believed that estrogen replacement in early postmenopausal women without coronary artery disease may reduce cardiovascular events and mortality, but a study of late postmenopausal women with coronary artery disease showed increased cardiovascular events during the first 2 years of hormone replacement therapy and no hip or other fracture reduction benefit [54]. Another study [55] showed a nonsignificant reduction in nonvertebral fracture risk in postmenopausal women treated with hormone replacement therapy. Estrogen replacement may be most effective if started at menopause, rather than later in postmenopausal life [56]. Common side effects of estrogen replacement include breast tenderness, vaginal bleeding or spotting, nausea, and increased risk of deep venous thrombosis.

### Selective Estrogen Receptor Modulator

Raloxifene is a selective estrogen receptor modulator (SERM) approved for both prevention and treatment of postmenopausal osteoporosis. This compound acts as an estrogen agonist on bone cells and in lipid metabolism [57] and probably in the cardiovascular system, but as an estrogen antagonist at breast, uterine, and perhaps hypothalamic tissues. Raloxifene 60 mg/day for 3 years reduced new morphometric vertebral fractures by 55% in postmenopausal women with low bone density and no prevalent vertebral fractures, and by 30% in women with prevalent vertebral fractures [58]. Raloxifene is contraindicated in patients with a history of deep venous thrombosis or pulmonary embolus. Raloxifene may reduce the risk of breast cancer [59] and cardiovascular morbidity and mortality, although this is not yet proven conclusively. Common side effects of raloxifene include hot flashes and increased risk of deep venous thrombosis.

### Calcitonin

Recombinant salmon calcitonin nasal spray is approved for treatment, but not prevention, of postmenopausal osteoporosis. Nasal spray calcitonin treatment for 5 years resulted in stable bone mineral density and a 33% reduction in vertebral fracture risk in postmenopausal women [60–62]. The effect of salmon calcitonin on other types of fractures is not yet certain, although it is likely to be beneficial. The most common side effect of salmon calcitonin nasal spray is nasal irritation.

### Bisphosphonates

Bisphosphonates are currently the most potent antiresorptive agents available for treatment of postmenopausal osteoporosis. Oral alendronate may be used daily (5 or 10 mg/day) or once weekly (35 or 70 mg/week) for prevention or treatment of postmenopausal osteoporosis [63–65]. Oral risedronate may be used daily (5 mg/day) or once weekly (35 mg/week) for prevention or treatment of postmenopausal osteoporosis [66–68]. Both are approved for prevention and treatment of postmenopausal osteoporosis. These drugs reduce fracture risk at vertebral and nonvertebral sites by about 50% to 60%. Daily oral alendronate [69] and risedronate [70] are also approved for prevention and treatment of glucocorticoid-induced osteoporosis, although it is likely that once weekly oral alendronate and risedronate also prevent and treat glucocorticoid-induced osteoporosis. Oral etidronate is given in a cycle of 400 mg/day for 2 weeks followed by 10 weeks of calcium supplement alone; this cycle is repeated 4 times per year. However, etidronate has not been approved for use in postmenopausal or glucocorticoid-induced osteoporosis, although it may be used for these purposes [71,72]. Common side effects of oral bisphosphonates include gastroesophageal irritation and bone pain.

Etidronate, pamidronate, and zoledronic acid [73] are intravenous bisphosphonates available in the United States. None has been approved for use in osteoporosis, although they may be used for this purpose in patients with severe osteoporosis. 

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**Table 3. Agents Approved for Prevention and Treatment of Osteoporosis**

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Estrogen/hormone replacement therapy</td>
<td>Raloxifene 60 mg/day</td>
</tr>
<tr>
<td>Raloxifene 60 mg/day</td>
<td>Fosamax 10 mg/day or 70 mg/week</td>
</tr>
<tr>
<td>Fosamax 5 mg/day or 35 mg/week</td>
<td>Risedronate 5 mg/day or 35 mg/week</td>
</tr>
<tr>
<td>Risedronate 5 mg/day or 35 mg/week</td>
<td>Miacalcin nasal spray 200 U/day</td>
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</table>
osteoporosis who are unable to tolerate any of the approved agents. Common side effects of the intravenous bisphosphonates include flu-like myalgias, low-grade fever, and bone pain. Eye inflammation can occur rarely with pamidronate.

**Combination and New Therapies**

Although several of these agents have been tried in combination in small studies (eg, alendronate and estrogen replacement [74–77]), none is approved for use in combination therapy. Combination therapy with alendronate and raloxifene [78] and etidronate and estrogen replacement [79], similar to combination therapy with alendronate and estrogen replacement, cause small incremental changes in BMD compared to increases in BMD induced by monotherapy. None of the studies has demonstrated differences in fracture risk reduction between monotherapy and combination therapy.

Intermittent recombinant human parathyroid hormone (PTH) (1-34) is likely to be the first anabolic agent for treatment of postmenopausal and other forms of osteoporosis. Daily subcutaneous injection of recombinant human PTH (1-34) 20 µg significantly increases BMD and decreases fractures [80].

**Treatment of Osteoporosis**

Due to the severity of the patient’s osteoporosis and her fracture history, as well as her need for ongoing glucocorticoid therapy for inflammatory polyarthritis, she is started on alendronate 70 mg once a week, after being advised of appropriate precautions. She is advised to walk for exercise for at least 3 hours per week. She continues her total daily elemental calcium intake of 1500 mg and begins taking 2 multivitamins each day to provide vitamin D 800 IU/day, as is appropriate for a patient on chronic glucocorticoid therapy.

- If the patient had presented without fractures, would the therapeutic approach have been different?

If this patient had the same clinical presentation without vertebral fractures, she would be advised to take the same therapy because of her ongoing use of glucocorticoid therapy. If she had a similar presentation without fractures or need for glucocorticoid therapy, she would likely be advised to take the same therapy, due mainly to the severity of her bone loss. If she had a similar presentation without fractures or need for glucocorticoid therapy and had less severe bone loss, she could consider other therapies as initial treatment. Oral bisphosphonates are the most potent osteoporosis therapies available, and given the current uncertainties regarding the effectiveness and side effects of estrogen or hormone replacement, it is clear that bisphosphonates are first-line therapy in many situations. The most common reasons oral bisphosphonates may not be first-line therapy in postmenopausal women are presence of contraindications, typically due to gastroesophageal irritation or allergy, need for extraskeletal benefits, and cost.

**1 Year Later**

The patient tolerates alendronate without difficulty and has no subsequent fractures. Her glucocorticoid therapy is slowly tapered to 8 mg/day due to intermittent polyarthritis symptoms. She returns for a repeat BMD test 1 year after starting therapy to make sure her osteoporosis is improving. Repeat lumbar spine BMD is 0.695 g/cm² (T score –3.9, Z score –2.4), and left femoral neck BMD is 0.650 g/cm² (T score –2.4, Z score –0.6).

Due to the unexplained slower than expected increase in her BMD, the patient is reevaluated for secondary causes of osteoporosis. Her serum calcium, phosphorus, alkaline phosphatase, and creatinine are mid-normal, but her PTH level is still increased at 7.1 pmol/L. She has faithfully maintained a total daily elemental calcium intake of 1500 mg and vitamin D supplement of 800 IU over the last year, and her serum 25-hydroxyvitamin D level is still mid-normal at 28 ng/dL. 24-hour urinary NTx-telopeptide is in the low-normal range for premenopausal women, appropriate for her alendronate therapy. However, her 24-hour urinary calcium is still increased at 350 mg, despite resolution of her primary hyperparathyroidism. Repeat radiograph of the kidneys, ureters, and bladder with tomograms reveals 2 new tiny calcium-containing kidney stones in the left kidney, not documented a year earlier.

- When should BMD measurements be repeated?
- How are biochemical markers of bone turnover used in the management of patients with postmenopausal osteoporosis?

Controversy exists as to when BMD measurements should be repeated, and whether repeat testing is cost-effective. Most often BMD measurements are repeated 2 years or more after the initial measurement to allow time for detection of significant changes in BMD. However, BMD measurements may be repeated within 6 months in patients receiving glucocorticoid therapy at doses of 7.5 mg/day or greater for 3 or more months, at least until the BMD is stable, and patients with significant bone loss and fractures may have repeat BMD testing sooner than 2 years to verify that their BMD is.
improving as expected on therapy. Some clinicians take the position that repeat BMD testing is not necessary due to the effectiveness of the therapies currently available for postmenopausal osteoporosis.

Serum and urine tests have been developed to assess bone metabolism, but none of the currently available serum or urine biochemical markers of bone turnover can serve as a substitute for bone density. The available urinary markers of bone resorption include N-telopeptide of type I collagen (NTx-telopeptide), and total and free pyridinoline and deoxypyridinoline. Serum markers of resorption are being developed because of the large coefficient of variation of urinary markers of resorption. Serum markers of bone formation include osteocalcin, bone-specific alkaline phosphatase, and procollagen type I extension peptides. Markers of bone turnover may be used clinically to document the effect of antiresorptive therapy in individual patients, as in this patient, and possibly to predict which patients with postmenopausal osteoporosis will benefit from antiresorptive therapy [81].

Further Treatment

The patient is diagnosed with idiopathic hypercalciuria, since it is unlikely her prednisone dose of 8 mg/day is responsible alone for her hypercalciuria. She is restarted on hydrochlorothiazide 25 mg/day, and repeat 24-hour urinary calcium 1 month later is 150 mg. Repeat serum calcium and PTH levels are normal at 9.5 mg/dL and 3.2 pmol/L, respectively.

She returns for follow-up 1 year later. She is tolerating her medications without difficulty, and her prednisone dose is further decreased to 5 mg/day. All serum and urinary chemistries are within normal range, and her repeat lumbar spine BMD is 0.601 g/cm² (T score –2.8, Z score –1.5), and the left femoral neck BMD is 0.580 g/cm² (T score –1.8, Z score –0.1). Repeat radiograph of her kidneys, ureters, and bladder is negative. She is advised to continue her regimen.

The patient’s excellent increase in BMD is attributed to optimization of her osteoporosis regimen and correction of all identifiable secondary causes of osteoporosis. In retrospect, while it is possible that her slow response to alendronate in her first year of therapy was normal (since some patients respond to oral bisphosphonate slowly in the first year), it is likely that the failure to recognize and treat her idiopathic hypercalciuria after cure of her primary hyperparathyroidism was a significant contributor to her apparent lack of response.

Summary

Postmenopausal osteoporosis is a public health problem that is frequently unrecognized because it does not cause symptoms until fractures develop. Strategies to prevent the development of postmenopausal osteoporosis must begin with adequate dietary calcium and vitamin D intake and exercise in the premenopausal years, as well as avoidance of environmental and other factors known to cause bone loss. At menopause, women should review their lifestyle choices and habits to determine whether changes would be beneficial. Consideration of BMD testing is appropriate for postmenopausal women aged 65 years or older without risk factors for osteoporosis, or younger postmenopausal women with risk factors. If significant bone loss is detected, consideration should be given to evaluating for secondary causes of bone loss. Once secondary causes are recognized and treated, effective therapies can be used to significantly improve BMD and reduce the likelihood of future fractures.

The pathophysiology of postmenopausal osteoporosis continues to be an area of active investigation, with future therapies likely to be based on recognized and newly discovered mechanisms of postmenopausal bone loss. Several selective estrogen receptor modulators, and at least 1 intravenous bisphosphonate, are under investigation for use in postmenopausal osteoporosis. Anabolic therapies in the form of new PTH analogues will likely be available in the near future, with other anabolic agents to come in the future.

Corresponding author: Bart L. Clarke, MD, Division of Endocrinology, Metabolism, Diabetes, and Nutrition, Mayo Clinic W-18B, 200 1st Street SW, Rochester, MN 55905, Clarke.Bart@Mayo.edu.

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EVALUATION FORM: Diagnosis and Management of Postmenopausal Osteoporosis

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Part 1. Please respond to each statement.

<table>
<thead>
<tr>
<th>Statement</th>
<th>Strongly Agree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>I was provided with new information pertinent to my practice.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I reaffirmed a specific skill or knowledge.</td>
<td></td>
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<tr>
<td>This article will help with clinical decision making.</td>
<td></td>
<td></td>
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<tr>
<td>Relevant clinical outcomes are addressed.</td>
<td></td>
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<tr>
<td>The case is communicated in a manner that kept my interest.</td>
<td></td>
<td></td>
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<tr>
<td>The case presentation is realistic and effective.</td>
<td></td>
<td></td>
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<tr>
<td>I could easily interpret the tables and figures.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My attitude about this topic changed in some way.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional comments: ______________________________________________________________________________________
________________________________________________________________________________________________________

Part 2. Please complete the following sentence.
As a result of reading this case study, I . . .

- see no need to change my practice.
- will seek more information before modifying my practice.
- intend to change the following aspect(s) of my practice: (Briefly describe)

________________________________________________________________________________________________________
________________________________________________________________________________________________________

Signature: ___________________________ Date: ___________________________

Part 4. Identifying information: Please PRINT legibly or type the following:
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