Treating osteoporosis in postmenopausal women: A case approach

**ABSTRACT**

We now have several agents of different classes for treating postmenopausal osteoporosis. In this paper, a case report serves as the focus for a discussion of the risk factors for postmenopausal osteoporosis and of the available therapies.

**KEY POINTS**

The National Osteoporosis Foundation recommends bone mass screening for postmenopausal women younger than 65 years with risk factors for osteoporosis, and for all women older than 65.

Patients at risk should consider a regimen of weight-bearing exercise, weight gain if necessary, and changes in the home to reduce the risk of falls.

Most patients need to increase their calcium and vitamin D intake, and may need to have their other medications altered to reduce problems with balance.

The bisphosphonates alendronate and risedronate reduce the risk of vertebral and nonvertebral fractures, with benefits documented for at least 7 years. They are now available in once-weekly formulations.

The anabolic agent teriparatide also reduces fracture risk, but its long-term effects are unknown.

All of the available agents seem to have less of an effect on the risk of nonvertebral fractures than on vertebral fractures.

A 79-YEAR-OLD WHITE WOMAN presents with back pain.

The patient is a widow and lives alone, spending most days watching television. Six months ago she fractured a rib after slipping on a throw rug on a hardwood floor. She has had hypertension for 5 years and depression for 1 year. She went through menopause at age 48 and was not treated with hormone replacement. She has a family history of osteoporosis. She does not smoke.

**Medications.** She takes a sedative for insomnia and an antihypertensive medication. She reports occasional dizziness, attributed to postural hypotension resulting from antihypertensive treatment.

**Height:** 156 cm (62 inches; 2 inches less than 10 years ago); weight 55 kg (121 lb).

**Laboratory results:**
- Serum calcium and thyroid function normal
- 25-hydroxycholecalciferol borderline low
- Parathyroid hormone level normal.

**Spinal radiograph.** Multiple compression fractures and multifocal vertebral degenerative changes.

**A MAJOR PUBLIC HEALTH PROBLEM**

Osteoporosis and osteopenia affect almost 44 million people age 50 and older in the United States, approximately 80% of whom are postmenopausal women. Both conditions increase susceptibility to fracture.
Approximately 700,000 osteoporosis-related vertebral fractures occur each year in the United States. Although fracture rates are highest in women with osteoporosis defined by bone density (T score –2.5 or below), the National Osteoporosis Risk Assessment (NORA) study found that most fractures (82%) occur in women with peripheral bone mineral density T scores greater than –2.5. Osteoporotic fractures are associated with increased morbidity and mortality, a compromised quality of life, and an estimated $17 billion in direct medical expenditures annually.

Too often, postmenopausal osteoporosis remains undiagnosed until a fragility fracture occurs. At this point, women are likely to sustain more fractures, and morbidity and mortality rates climb.

<table>
<thead>
<tr>
<th>Table 1</th>
<th><strong>Risk factors for low bone mass</strong></th>
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| **Nonmodifiable** | White race  
Female sex  
Family history of osteoporosis  
Previous atraumatic fracture  
Advanced age |
| **Potentially modifiable** | Estrogen deficiency  
Low calcium intake (lifelong)  
Current cigarette smoking  
Low body weight (< about 127 pounds)  
Excessive alcohol intake  
Inadequate physical activity  
Poor health  
Frailty |
| **Medications** | Glucocorticoids  
Anticonvulsants  
Excess thyroid hormone  
Heparin |
| **Diseases** | Rheumatoid arthritis  
Hyperthyroidism  
Hyperparathyroidism  
Cushing disease  
Lymphoma or leukemia  
Myeloma  
Sarcoidosis  
Malabsorption, gastrectomy, or malnutrition |

Fracture risk doubles for each standard deviation below the mean.

**Who should be screened?**

Risk factors help in assessing whether a patient may have low bone mass or be at risk for fracture and in deciding if he or she should be screened for osteoporosis (Table 1). The National Osteoporosis Foundation recommends bone mass measurements for:

- Postmenopausal women younger than 65 years with at least one risk factor for osteoporosis (other than being white) or with a fracture
- All women age 65 and older regardless of their risk profile

By and large, screening is best done with tabletop measurements of bone density in both the hip and spine by dual-energy x-ray absorptiometry (DXA). Another screening tool, ie, ultrasonography of the heel, can be used for mass screening if DXA is not available. Although a low reading by ultrasonography and DXA of the finger or wrist is predictive of future fractures, the correlation is less precise than with DXA of the hip and spine.

Our patient presents with vertebral fractures and several other risk factors: advanced age, height loss, a recent fracture, family history of osteoporosis, estrogen deficiency, white race, low body weight, low level of physical activity, and vitamin D deficiency. She is also at higher risk for falling because of instability exacerbated by her medications. However, nothing in her medical history suggests secondary osteoporosis, eg, due to glucocorticoid therapy, and her normal parathyroid hormone level rules out secondary hypoparathyroidism.

**Case continued**

The patient undergoes bone density measurement with DXA. Her T score is –2.8 at the lumbar spine and –3.0 at the femoral neck.

**Bone mass and history determine severity**

Bone density measurements can be taken of the spine, hip, or wrist; when values are available for more than one site, risk is determined by the lowest value.

Fracture risk approximately doubles for each standard deviation below the mean.

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**TABLE 1**

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Hyperthyroidism  
Hyperparathyroidism  
Cushing disease  
Lymphoma or leukemia  
Myeloma  
Sarcoidosis  
Malabsorption, gastrectomy, or malnutrition |
Furthermore, once a patient sustains a fracture, she is five times more likely to sustain another fracture within a year than is a woman without a fracture (FIGURE 1). In addition to previous fracture and low bone mineral density, the NORA study found that poor health status and mobility also contribute to fracture risk.

Our patient has severe osteoporosis: she has both a history of fracture and spine and hip bone densities more than 2.5 standard deviations below the mean for young women (TABLE 2). Her low bone density, combined with multiple (more than five) risk factors for fracture, make her risk of hip fracture 10 times higher than for a woman with low bone mineral density but with no more than two risk factors. Her life expectancy is also shortened—the odds for survival decrease with more vertebral or hip fractures.

Therefore, she has a clear and urgent need for treatment to prevent additional fractures.

### NONPHARMACOLOGIC TREATMENTS

**Supplemental calcium and vitamin D**

This patient’s housebound lifestyle may limit her sun exposure, an important factor in vitamin D metabolism. Calcium and vitamin D supplementation is recommended to bring intake levels to the following:

- Elemental calcium 1,500 mg/day
- Vitamin D 400–1,000 IU/day.

If the parathyroid hormone level is elevated, a higher dose of vitamin D might be warranted (50,000 IU once or twice a week for 3–6 months with careful monitoring of serum calcium levels and a repeat testing of vitamin D and parathyroid levels at 3–6 months).

In women with symptomatic osteoporosis, calcium and vitamin D supplementation alone do not reduce the risk of vertebral fractures, but they do increase the efficacy of osteoporosis medications.

**Other measures**

**Encourage exercise.** Weight-bearing exercise for 30 to 60 minutes at least 3 times a week improves muscle strength and balance, reducing the risk of falling.

**Manage depression.** This patient’s depression should be managed with counseling, anti-depressants, or both. This may help increase appetite and physical activity.

**Remove hazards at home,** such as throw rugs, which are easily slipped on.

**Adjust current medications** if necessary. This patient’s antihypertensive and sedative medications should be changed or the dosages adjusted to help avoid dizziness and postural hypotension.

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**FIGURE 1.** Relative risk of subsequent vertebral fractures over a 1-year observation period, stratified by the number of vertebral fractures at baseline.

**TABLE 2**

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>T SCORE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; –1</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>–1 to −2.499</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>≤ −2.5</td>
</tr>
<tr>
<td>Severe osteoporosis</td>
<td>≤ 2.5 with fragility fractures</td>
</tr>
</tbody>
</table>

*Standard deviations below the mean values for a healthy young adult.
Consider hip protectors to reduce the impact of a fall.\textsuperscript{21}

\section*{SEVERAL MEDICATIONS AVAILABLE}

This patient has vertebral fractures and low bone density in the hips and spine, and therefore she requires medication. (In general, patients with a T score of less than $–2.0$, or less than $–1.5$ with risk factors, should be considered for management with medication.)

Several medications are available in the United States for treating postmenopausal osteoporosis (\textit{TABLE 3}). Which one to prescribe depends on how effective it is, how quickly benefits are realized, and how well the patient tolerates it. Patients must comply with treatment over the long term to benefit.

The most clinically relevant measure of a medication’s efficacy is how well it reduces fracture risk. Although bone density is a good predictor of fracture risk and can determine the need for osteoporosis treatment, the increases in density that are associated with medications do not completely explain how they protect against fractures.\textsuperscript{22–24}

\textbf{\textit{TABLE 3}} compares the efficacy of different medications in clinical trials.

\section*{BISPHOSPHONATES}

The bisphosphonates currently available in the United States are alendronate and risedronate. A third agent, ibandronate, was recently approved by the US Food and Drug Administration for the treatment and prevention of postmenopausal osteoporosis. Its early trial data are promising,\textsuperscript{25} but it is not yet available for clinical use.

**Bisphosphonates prevent vertebral fractures**

Alendronate and risedronate reduce the incidence of new vertebral fractures by 40\% to 50\% after 3 years of treatment in postmenopausal women with osteoporosis, including those with radiographically verified vertebral fractures at baseline.\textsuperscript{26–29}

\textbf{Short-term benefit.} The benefit becomes apparent early on, which is especially important to patients who already have vertebral fractures, in view of their high risk for subsequent fractures. A post hoc analysis found a lower relative risk of clinical vertebral fractures after 1 year of alendronate therapy ($59\%$, $P < .001$) in patients with at least one vertebral fracture or a T score of less than $–2.5$.\textsuperscript{30}

In two prospective studies in postmenopausal women with osteoporosis who had at least one vertebral fracture at baseline, risedronate reduced the risk of morphometric vertebral fractures at 1 year by 65\% and 61\%.\textsuperscript{27} Pooled data from risedronate trials demonstrated a reduction ($P < .01$) in clinical vertebral fracture risk as early as 6 months after start of treatment.\textsuperscript{31} Among women with two or more radiographically determined vertebral fractures at baseline, a 68\% ($P < .001$) risk reduction in new vertebral fractures was observed after 1 year of treatment with risedronate.\textsuperscript{32}

\textbf{Long-term benefit.} Patients had 63\% fewer symptomatic vertebral fractures on alendronate vs placebo during a 4-year period in the Fracture Intervention Trial (FIT) ($P < .01$).\textsuperscript{33} Skeletal benefits have been reported for up to 10 years, with bone density increased slightly in the spine and maintained in the hip during treatment years 4 to 10 (fracture risk reduction was not calculated because the
extension of the trial was not placebo-controlled).34,35

A placebo-controlled 2-year extension of the Vertebral Efficacy With Risedronate Therapy-Multinational (VERT-MN) study of 265 patients showed that morphometric vertebral fracture risk was reduced by 59% (P = .01) during years 4 and 5 with daily risedronate vs placebo.36 An open-label 2-year extension showed a sustained effect with a nearly constant incidence of vertebral fractures throughout treatment (4.7% for years 0–3, 5.2% for years 4–5, and 3.8% for years 6–7).37

Once-a-week pills
Risedronate and alendronate are available as once-weekly formulations, which have demonstrated similar benefits in lumbar spine and hip bone density and in bone turnover markers compared with their once-a-day counterparts.38–40 The incidence of clinical vertebral fractures was also similar for both formulations of alendronate after 1 and 2 years of therapy.38,40 A post hoc analysis found that the 1-year risk of morphometric vertebral fractures was reduced by 77% (P = .018) for patients on once-weekly risedronate vs a historical placebo control group.41

Less effect on nonvertebral fracture risk
There is conflicting evidence about whether alendronate reduces the risk of nonvertebral fractures. The FIT authors found no significant risk reduction.26,42 However, the Fosamax International Trial (FOSIT) found that it reduced the risk over 1 year by 47% (P = .021) in postmenopausal women with low bone mass (T score –2 or below).43 Another post hoc analysis also showed that nonvertebral fracture risk declined after 2 years (26%, P = .011).30

Risedronate reduced nonvertebral fracture risk by up to 39% in long-term prospective clinical trials.27,28,44 Pooled results from four major trials indicate that risk is reduced by 74% (P = .001) at 1 year and that risk reduction is evident as early as 6 months.45

**Hip fracture risk.** FIT found that in 2,027 women with at least one existing vertebral fracture, alendronate reduced hip fracture risk by 51% (P = .047).26 However, risk was

### Table 4

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Duration</th>
<th>Reduction in fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risedronate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harris et al27</td>
<td>2,458</td>
<td>3 years</td>
<td>41%*</td>
</tr>
<tr>
<td>Reginster et al28</td>
<td>1,226</td>
<td>3 years</td>
<td>49%*</td>
</tr>
<tr>
<td>McClung et al44,66</td>
<td>9,331</td>
<td>3 years</td>
<td>55%*</td>
</tr>
<tr>
<td><strong>Alendronate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black et al26</td>
<td>2,027</td>
<td>3 years</td>
<td>47%*</td>
</tr>
<tr>
<td>Cummings et al42</td>
<td>4,432</td>
<td>4 years</td>
<td>44%*</td>
</tr>
<tr>
<td>Liberman et al29</td>
<td>994</td>
<td>3 years</td>
<td>48%*</td>
</tr>
<tr>
<td><strong>Raloxifene</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ettinger et al53</td>
<td>7,705</td>
<td>3 years</td>
<td>30%*</td>
</tr>
<tr>
<td><strong>Salmon calcitonin nasal spray</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chestnut et al57</td>
<td>1,255</td>
<td>5 years</td>
<td>33%*</td>
</tr>
<tr>
<td><strong>Teriparatide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neer et al58</td>
<td>1,637</td>
<td>21 months</td>
<td>65%*</td>
</tr>
</tbody>
</table>

*Statistically significant difference compared with placebo group (P < .05)
not reduced in subjects with low bone density
in the femoral neck or in subjects who had no
vertebral fractures at baseline.42

In a prospective, double-blind, placebo-
controlled trial,44 risedronate reduced the
incidence of hip fracture by 40% (P = .009) in
5,445 women with confirmed osteoporosis
(mean T scores about –2.7 to –2.9) and by
60% (P = .003) in 1,703 women who had ver-
tebral fractures at baseline. However, it did
not significantly reduce hip fractures in a
group of women over age 80 without con-

These data underscore that hip fractures
and falls pose a serious risk to older women,
who should be screened with DXA to estab-
lish the diagnosis of osteoporosis. The data
also underscore the need to prevent falls in
this population.

Upper GI side effects of bisphosphonates

To reduce the risk of esophageal irritation,
patients should be advised not to lie down for
30 minutes after they have taken their
dose.46,47

After alendronate was introduced in 1995,
there were numerous reports of upper gastroin-
testinal (GI) problems, including ulcerative or
erosive esophagitis and esophageal stricture.
These occurred more often and more severely
than was predicted from clinical trials,48 in
which the reported rates of upper GI adverse
events for patients taking either alendronate or
risedronate were similar to those of place-
bo.26–29,42,44

However, a newer review indicates that
reports of esophagitis have declined, possibly
because physicians have become more aware
of the problem and are advising their patients
about how to take these medications.49

Is risedronate better tolerated than alen-
dronate? It is possible that subjects in the clin-
ical trials of risedronate were more likely than
those in the alendronate trials to have had a
history of GI problems at baseline. Rised-
ronate trials did not exclude patients with
acute GI disorders or those taking acid-sup-
pressive therapy or nonsteroidal anti-inflam-
matory drugs (including aspirin),27,28,44 while
some of the alendronate trials did exclude
women with active peptic ulcer disease26,29,42
or dyspepsia.26,42

A retrospective analysis of a claims data-
base of nearly 4,000 men and women older
than 65 years found that once-daily rised-
ronate was associated with significantly fewer
GI adverse events and medical costs related to
these events than once-daily and once-weekly
alendronate.30,51 Moreover, risedronate recipi-
ents in these analyses were more likely to have
had GI problems before treatment than were
the alendronate recipients.

However, pooled data from 10,068
patients (> 98% postmenopausal women)
treated with risedronate or placebo for up to 3
years showed no significant difference in the
incidence of upper GI adverse events overall
or after stratification for upper GI disease or
use of nonsteroidal anti-inflammatory drugs,
H2-blockers, or proton pump inhibitors.52

It is difficult to be certain whether rised-
ronate is more tolerable than alendronate with-
out head-to-head clinical studies. Regardless,
now that once-weekly formulations of both
medications are available, patients may find it
easier to comply with instructions and mini-
mize potential GI problems.

RALOXIFENE

In a large clinical trial of 7,705 subjects (about
one third with an existing vertebral fracture at
baseline), daily raloxifene for 3 years signifi-
cantly reduced the incidence of vertebral frac-
tures by 30% overall (risk was reduced 30% for
those with a vertebral fracture at baseline and
50% for those without, both P < .05).53

A post hoc analysis of data from this study
showed daily raloxifene reduced the risk of clinical
vertebral fractures at 1 year by 68% (P < .05)
in the overall population and 66% (P < .05) in
women with a baseline vertebral fracture.54

The incidence of nonvertebral fractures
was similar with raloxifene or placebo in the
overall study group. However, in a post hoc
analysis, those with a severe vertebral fracture
at baseline (> 40% decrease in vertebral
height) had a 47% reduction (P = .046) in
overall nonvertebral fracture risk after 3 years
of daily raloxifene.55

Adverse effects of raloxifene

Daily raloxifene is associated with an increased
incidence of influenza syndrome, hot flashes,
leg cramps, and peripheral edema compared with placebo. It is also associated with a higher risk of thromboembolic events, with rates similar to those reported for postmenopausal women receiving estrogen therapy.

**SALMON CALCITONIN**

Salmon calcitonin nasal spray reduced the 5-year risk of new vertebral fractures by 33% ($P = .03$) in postmenopausal women with vertebral fractures at baseline at the approved daily dose of 200 IU (but not at 100 IU or 400 IU) vs placebo. It did not reduce the risk of nonvertebral fractures, including hip fractures.

The dropout rate was 59% over 5 years and was similar in all treatment groups. Salmon calcitonin nasal spray was generally well tolerated, but a slight increase in rhinitis was reported in treated patients vs placebo.

**TERIPARATIDE**

Teriparatide, a formulation of recombinant human parathyroid hormone (1-34), induces bone formation. In contrast, the other agents inhibit bone resorption.

In a study in 1,637 postmenopausal women with at least one vertebral fracture, teriparatide (20 µg subcutaneously once a day) reduced the risk of new morphometric vertebral fractures by 65% ($P < .001$) and of nonvertebral fractures by 35% ($P = .04$) over a median follow-up of 21 months. The risk of nonvertebral fractures considered to be fragility fractures was reduced by 53% ($P = .02$).

Dizziness and leg cramps were reported in significantly more patients with teriparatide treatment than with placebo.

The US Food and Drug Administration recommends the use of teriparatide for no more than 2 years, as clinical data are available for only 21 months.

**HORMONE THERAPY**

The Women's Health Initiative trial found that hormone therapy reduced the risk of hip and spine fractures. However, risks associated with hormone therapy may be greater than previously thought, and it should be used only as long as is necessary to treat menopausal symptoms.

**COMBINATION THERAPY**

In theory, it is possible that combinations of different medications may confer additive or synergistic benefits. However, recent data indicate that alendronate blunts the effects of teriparatide, so these two agents should not be used simultaneously.

More studies are needed to determine whether different combinations of medications are beneficial.

**CASE REVISITED**

In our patient, who has severe osteoporosis and multiple risk factors, once-daily or once-weekly bisphosphonate therapy is recommended as first-line therapy to reduce fracture risk.

Teriparatide is a reasonable alternative if she has a poor response (see below) or does not tolerate either bisphosphonate. Its appropriate role is still evolving. It may be useful as initial therapy followed by an antiresorptive agent (ie, a bisphosphonate) in patients at high risk.

Raloxifene and salmon calcitonin are other alternatives, but neither has reduced the risk of nonvertebral fractures in postmenopausal women with osteoporosis in prospective studies.

Hormone therapy is not indicated for the treatment of postmenopausal osteoporosis, and therefore it is not an option for this patient.

**Follow-up DXA for patients on therapy**

Depending on the coefficient of variation of the particular DXA device used, an improvement of less than 2% per year would be considered a nonresponse.

The frequency of repeated DXA determinations depends on the severity of the initial measurement. For most patients, repeated DXA every 2 years allows enough time between measurements to allow significant expression of change of bone density. But if a patient has severe osteoporosis with fractures or has secondary causes such as steroid exposure or hyperparathyroidism, then yearly or even more frequent determinations may be warranted.
REFERENCES


46. Fosamax (alendronate sodium) [full prescribing information]. West Point, PA: Merck & Co Inc; 2003.
47. Actonel (risedronate sodium) [full prescribing information]. Cincinnati, OH: Procter & Gamble Pharmaceuticals; 2003.

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