Strategies for the prevention and treatment of osteoporosis during early postmenopause

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Received for publication April 20, 2005; accepted August 18, 2005

During the perimenopause, both the quantity and quality of bone decline rapidly, resulting in a dramatic increase in the risk of fracture in postmenopausal women. Although many factors are known to be associated with osteoporotic fractures, measures to identify and treat women at risk are underused in clinical practice. Consequently, osteoporosis is frequently not detected until a fracture occurs. Identification of postmenopausal women at high risk of fracture therefore is a priority and is especially important for women in early postmenopause who can benefit from early intervention to maintain or to increase bone mass and, thus, reduce the risk of fracture. Most authorities recommend risk-factor assessment for all postmenopausal women, followed by bone mineral density measurements for women at highest risk (ie, all women aged ≥65 years, postmenopausal women aged <65 years with ≥1 additional risk factors for osteoporosis, and postmenopausal women with fragility fractures). All postmenopausal women can benefit from nonpharmacologic interventions to reduce the risk of fracture, including a balanced diet with adequate intake of calcium and vitamin D, regular exercise, measures to prevent falls or to minimize their impact, smoking cessation, and moderation of alcohol intake. Several pharmacologic agents, including the bisphosphonates (eg, alendronate, risedronate, and ibandronate) and the selective estrogen receptor modulator, raloxifene, have been shown to increase bone mass, to reduce fracture risk, and to have acceptable side-effect profiles. Women who have discontinued hormone therapy are in particular need of monitoring for fracture risk, in light of the accelerated bone loss and increased risk of fracture that occurs after withdrawal of estrogen treatment.

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After peak bone mass is achieved during the third decade of life, bone architecture is maintained by a constant remodeling process. Osteoclasts attach to a specific area of bone, remove old bone (resorption pit), then osteoblasts move in and fill this pit with new bone. The balance between these processes shifts at menopause,1–4 and women typically undergo a rapid phase of bone loss that begins approximately 2 to 3 years before the cessation of menses and continues for up to 5 years.
postmenopause.⁵⁻⁷ Although the decreased concentrations of circulating estrogen that characterize meno-
pause and the rapid phase of bone loss are chiefly
responsible for the process,⁵ many other factors are as-
associated with increased fracture risk.⁸ These factors in-
clude prior fragility fracture, advanced age, a family
history of osteoporotic fracture, and the use of certain
medications.¹,³ Additional predictors of bone loss and
fracture risk in early postmenopause include prolonged
low vitamin D and calcium intake and low body
weight.¹,⁵,¹⁰ Osteoporotic fractures are preventable;³
risk-factor assessment and methods to assess bone
mass are available for the identification of women at
risk, and management of osteoporosis is possible
through pharmacologic and nonpharmacologic mea-
sures.¹¹ Unfortunately, these measures are often under-
used, representing missed opportunities for prevention
and treatment of osteoporosis.¹² As a result, osteopo-
rosis frequently is not detected until the patient presents
with a fracture.¹ Moreover, even those patients who
do experience a fracture often do not receive subsequent
treatment for osteoporosis, leaving them at high risk for
future fractures.¹²,¹³

There are many factors that contribute to the less
than optimal identification and treatment of these
patients; the difference between best practice and clinical
practice with respect to the management of osteoporosis
are diverse. Women at risk of osteoporotic fracture may
fall into a health care gap between the obstetricians,
gynecologists, internists, and others, who are in a
position to detect and treat osteoporosis, thereby
preventing fractures, and the orthopedists who are
responsible for treating the fractures.¹²,¹⁴,¹⁵ Altern-
atively, some women may fall victim to the failure of
health care providers to initiate or alter intervention
strategies, despite changes in the patient’s health status
that would seemingly justify such action.¹²

To prevent the progression of osteoporosis and the
occurrence and recurrence of fracture in postmenopau-
sal women, primary health care providers must recog-
nize osteoporosis as a risk factor for fracture, just as
hypertension is a risk factor for stroke¹ and accordingly
intervene as early as possible to maximize the retention
and the enhancement of bone mass and the structural in-
tegrity of the skeleton.¹,³ This article will review current
strategies for the prevention and treatment of bone loss
during perimenopause and early postmenopause to reduce
the risk of osteoporotic fracture.

Identification of women at risk

Most authorities recommend risk-factor assessment for
all postmenopausal women, followed by bone mineral
density (BMD) testing for those women at highest risk
for osteopenia, osteoporosis, and fractures.¹⁴⁻⁶

The National Osteoporosis Foundation (NOF) rec-
ommends that the following women undergo BMD
testing:

- All women aged 65 years or older, regardless of other
  risk factors for osteoporosis;
- Postmenopausal women younger than 65 years with
  1 or more risk factors for osteoporosis (other than
  being white, postmenopausal, and female); and
- All postmenopausal women who have had a fragility
  fracture.¹

The recommendations of the North American Men-
opause Society (NAMS), the American Association of
Clinical Endocrinologists (AACE), and the American
College of Obstetricians and Gynecologists (ACOG)
regarding BMD measurements generally parallel those
of the NOF.²⁻³,⁶⁻¹⁷

Two different scoring methods—the T-score and the
Z-score—are commonly used by device manufacturers
in scoring dual-energy x-ray absorptiometry (DXA) scans,
both of which compare a woman’s BMD value with the
average value expected based on population norms, to
gauge the presence or absence of osteoporosis and to
determine the risk for fracture. The T-score quantifies
the difference between an individual’s BMD value and
the norm for “young normal” adults of the same sex and
ethnicity at peak bone mass. This difference is expressed
as standard deviations (SDs) above or below the mean.
A postmenopausal woman is considered to have a
normal BMD value if her T-score is −1.0 or above (no
lower than 1.0 SD below the BMD norm for “young
normal” women). A diagnosis of low bone mass, or
osteopenia, is assigned to women whose T-scores fall
between −1.0 and −2.5 SDs (between 1.0 and 2.5 SDs
below that of “young normal” women). A woman is
diagnosed with osteoporosis if her T-score is −2.5 or
lower (at least 2.5 SDs lower than the norm for “young
normal” women).¹⁸ The Z-score quantifies the difference
between an individual’s BMD value and the norm for
sex- and age-matched people.³ It should not be used
for the diagnosis of postmenopausal osteoporosis but
may be appropriate for determining whether additional
screening is necessary for secondary osteoporosis.¹⁹

Nonpharmacologic intervention

All women, regardless of menopausal status, should be
made aware of their risk of osteoporosis and of ways in
which they can reduce their risk of bone loss and fracture.
Communicating the value of bone health to minimize
fracture risk may motivate patients to make and maintain
lifestyle changes. Clinicians should discuss, in appropriate
detail, the range of nonpharmacologic approaches to
maintain bone health and to prevent osteoporotic frac-
ture with their patients (Table I). Ideally, the clinician’s
involvement at this important stage of a woman’s life will motivate her to make and sustain lifestyle changes relating to diet, exercise, tobacco and alcohol use, and approaches to fall prevention.

Calcium and vitamin D

Probably the easiest, least costly, and safest lifestyle modification to achieve is adequate intake of calcium and vitamin D.\(^1\)\(^,\)\(^2\) Although dietary sources of these nutrients are optimal,\(^1\) supplements should be used if diet alone cannot provide the recommended daily intake. The NOF recommends at least 1200 mg of dietary calcium and 400 to 800 IU of vitamin D each day.\(^1\) Based on levels of intake demonstrated in clinical trials to preserve calcium in the skeleton.\(^2\) Similarly, the National Academy of Sciences considers 1200 mg of calcium and 400 to 600 IU of vitamin D as adequate daily intakes of these nutrients for women aged 51 years or older.\(^2\)\(^1\)

Weight-bearing exercise

All postmenopausal women should be counseled regarding the benefits of regular physical exercise to achieve several objectives, including maintenance of muscle and bone strength through adulthood, reduction in the risk of fragility fractures, promotion of overall fitness, and improvement of quality of life.\(^2\)\(^2\)\(^-\)\(^4\) The skeletal benefits of weight-bearing exercise have been well documented in a multitude of randomized controlled trials.\(^2\)\(^5\)\(^-\)\(^7\) For example, the results of a prospective cohort study of more than 60,000 postmenopausal women (aged 40-77 years) showed that women who engaged in walking and other leisure-time activities were 55% less likely to suffer a hip fracture than sedentary women.\(^2\)\(^6\) In addition, The Erlangen Fitness Osteoporosis Prevention Study showed that aerobic, weight-bearing, strength training, and stretching exercises increased lumbar spine BMD by 1.3% over 14 months in postmenopausal women (up to 8 years postmenopause) who were receiving calcium and vitamin D supplementation compared with a 1.2% decrease in the control group.\(^2\)\(^7\) After 26 months, lumbar spine BMD was still higher in the exercise group (+0.7%) compared with an even further decrease in the control group (−2.3%).\(^2\)\(^8\) Although any increase in physical activity may be an improvement for currently sedentary women, the average older woman is not likely to exercise to the level needed to actually build bone. However, exercise is critical to strengthen muscles, improve balance, prevent falls, and a weekly exercise program ideally should incorporate at least 3 sessions lasting from 30 to 60 minutes each.

The relationship between exercise and hormone therapy (HT) on BMD in younger postmenopausal women was recently evaluated in the Bone, Estrogen, and Strength Training study.\(^2\)\(^9\) In this 12-month study, 320 women, who were 3 to 11 years postmenopausal (surgical or natural) and who were, on average, aged 56 years, were prospectively randomized within groups (HT or no HT) to participate in a supervised weight-bearing, weight-lifting program, or to continue their current level of physical activity.\(^2\)\(^9\) All women received calcium citrate 800 mg/d.\(^2\)\(^9\) After 12 months, women who exercised experienced significant \(P < .01\) mean increases in trochanter BMD (1.2%-2.1%) regardless of HT use, whereas women who received HT experienced significant \(P < .01\) increases in BMD at the lumbar spine (0.7%-0.8%) and total body (0.4%) regardless of exercise status.\(^2\)\(^9\) Women who neither exercised nor received HT generally lost BMD at all sites evaluated.\(^2\)\(^9\) Overall, these results suggest independent benefits of exercise and HT in early postmenopausal women receiving adequate calcium.\(^2\)\(^9\)

Fall prevention

Although younger postmenopausal women are at lower risk for falls and fall-related fracture than older postmenopausal women, fall prevention is an important consideration for all postmenopausal women. Therefore, NAMS recommends annual evaluation of a woman’s risk for falls.\(^2\) Several factors are correlated with increased

<table>
<thead>
<tr>
<th>Table I: Recommended nonpharmacologic interventions for the prevention of osteoporotic fracture(^1)(^,)(^2)(^,)(^2)(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Balanced diet including adequate protein, calcium 1200 mg/d, and vitamin D 400-600 IU/d</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Weight-bearing* activities</td>
</tr>
<tr>
<td>Muscle-strengthening activities</td>
</tr>
<tr>
<td>Smoking cessation</td>
</tr>
<tr>
<td>Reduction of excessive alcohol intake</td>
</tr>
<tr>
<td>Vision correction</td>
</tr>
<tr>
<td>Household/workplace management</td>
</tr>
<tr>
<td>Medication review to identify current medications that may be associated with dizziness or balance problems</td>
</tr>
</tbody>
</table>

* Non–weight-bearing exercise (eg, swimming) is of unknown benefit.
fall risk, including poor vision, muscle weakness or poor muscle coordination, dizziness, balance problems, and a personal history of falls, fainting, or loss of consciousness.\textsuperscript{2} Vitamin D deficiency, a common feature in postmenopausal women, is associated with increased body sway and a consequent increased risk of falls and fall-related fractures.\textsuperscript{30} Supplementation with vitamin D and calcium has been shown to reduce the risk of falling in elderly women (aged 85.3 years), possibly via improved musculoskeletal function.\textsuperscript{31} The use of a wide variety of medications, including sedatives, narcotic analgesics, antidepressants, anticholinergics, and antihypertensive agents, should be viewed as an additional risk factor for falls.\textsuperscript{2} In addition, safety hazards in the home and work environment, including obstacles and poor lighting, increase the risk of a fall.\textsuperscript{2} Specific steps should be taken to identify and reduce or eliminate, if possible, any of these risk factors. These steps may include checking and correcting vision, evaluating any neurologic problems, reviewing prescription medications for side effects that affect balance, and providing a checklist for improving safety at home. In addition, hip protectors should be considered for patients who have significant risk factors for falling or a history of hip fracture.\textsuperscript{1}

Other lifestyle changes

The use of tobacco or excessive alcohol consumption by postmenopausal women should be reviewed and addressed on an individual basis. Because smoking can reduce BMD and can increase fracture risk, in addition to its detrimental systemic effects,\textsuperscript{1,2} smokers should be encouraged to quit on their own or participate in a smoking cessation program. Although moderate levels of alcohol consumption (≤7 drinks per week) may not have an adverse physiologic effect on bone, excessive alcohol use does adversely impact bone health.\textsuperscript{1,2} Therefore, patients who drink excessively should be offered specific counseling and treatment to address this problem.\textsuperscript{1}

Pharmacologic intervention

Women with low bone density should be offered effective pharmacotherapy to reduce their risks of fracture and associated complications.\textsuperscript{1,2,16,17} According to the NOF and ACOG, candidates for pharmacologic intervention include postmenopausal women with T-scores below −2.0 by central DXA with no risk factors, postmenopausal women with T-scores below −1.5 by central DXA with 1 or more risk factors, and postmenopausal women with prior fragility fractures.\textsuperscript{1,16} Other authorities, including the World Health Organization, NAMS, and AACE designate an intervention threshold T-score of −2.5 SDs.\textsuperscript{2,11,17} However, therapy may be considered for women with borderline low BMD (eg, a T-score of −1.5) if 1 or more risk factors are present.\textsuperscript{2,11,17,32} Although medical treatment to prevent bone loss in peri-menopausal women with normal BMD values may seem reasonable in theory, clinical data supporting this approach are limited at this time.\textsuperscript{1}

Several pharmacologic options are now available for the prevention and/or treatment of postmenopausal osteoporosis based on their ability to increase BMD and to reduce the risk of fracture (Table II). The key clinical trials that achieved these endpoints involved older postmenopausal women (mean ages: 65-83 years) at high risk of fracture.\textsuperscript{33-46} Intervention trials also have been conducted in younger postmenopausal women (mean ages: 51-56 years) to assess the effect of various pharmacologic agents on BMD and markers of bone turnover.\textsuperscript{41-46} To date, there have been no intervention studies demonstrating a reduction in the risk of osteoporotic fractures in early postmenopausal women.

### Table II Marked pharmacologic options for the prevention and/or treatment of postmenopausal osteoporosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate\textsuperscript{104}</td>
<td>Treatment and prevention</td>
<td>Solution or tablet ≥30 min before first food or beverage of the day. Available in once daily or once weekly formulations.</td>
</tr>
<tr>
<td>Calcitonin\textsuperscript{89}</td>
<td>Treatment (women who are &gt;5 y postmenopause)</td>
<td>1 tablet daily, administered anytime of day.</td>
</tr>
<tr>
<td>Raloxifene\textsuperscript{105}</td>
<td>Treatment and prevention</td>
<td>1 tablet daily, administered anytime of day.</td>
</tr>
<tr>
<td>Risedronate\textsuperscript{106}</td>
<td>Treatment and prevention</td>
<td>1 tablet ≥30 min before first food or beverage of the day. Available in once daily or once weekly formulations.</td>
</tr>
<tr>
<td>Teriparatide\textsuperscript{98}</td>
<td>Treatment (women who are at high risk of fracture)</td>
<td>1 subcutaneous injection per day.</td>
</tr>
<tr>
<td>Estrogen plus progestin or estrogen alone\textsuperscript{56}</td>
<td>Prevention (women should be at significant risk of osteoporosis, and other medications should be inappropriate)</td>
<td>1 tablet per day.</td>
</tr>
</tbody>
</table>


Hormone therapy with estrogen plus progestin or estrogen alone

Mechanism of action

Estrogen therapy inhibits bone resorption by inhibiting osteoclast formation and function and prolongs the lifespan of osteoblasts and osteocytes. The combined effect produces a net increase in bone density.

Efficacy

Data from the large Women's Health Initiative (WHI), in which women with an intact uterus (mean age: 63 years) were randomly assigned to estrogen plus progestin, showed that HT increased total hip BMD and reduced the risk of fractures at the hip, vertebrae, and wrist. Similarly, the estrogen-alone component of the WHI, which involved women (mean age: 64 years) with prior hysterectomy, demonstrated a reduced rate of hip fracture. In addition, HT has been shown to reduce bone turnover and to increase BMD in early postmenopausal women. In 1 study, conjugated estrogens plus progesterone at various doses significantly increased BMD at the hip and spine by approximately 2% to 3% during 2 years of therapy (P < .001 vs placebo) in women who were up to 4 years postmenopause and who were aged 40 to 65 years. In another study, markers of bone turnover decreased in response to HT, and the magnitude of this effect correlated with gains in BMD at 1 year in women 6 months to 3 years postmenopause who were aged 40 to 58 years.

Safety

Once a mainstay of osteoporosis treatment and prevention, HT is now being intensively re-evaluated in light of the recent outcomes of the WHI. During the course of the estrogen plus progestin trial, evidence of an increased risk of breast cancer and of cardiovascular outcomes prompted the termination of this treatment group in 2002. In 2004, the estrogen-alone trial was stopped because of an increased risk of stroke and failure to lower the incidence of coronary heart disease. This turn of events led the investigators to conclude that HT should not be recommended for the prevention of osteoporosis in postmenopausal women unless the woman is at significant risk of osteoporosis and osteoporosis medications are unable to be considered.

The publication of the initial WHI findings in 2002 regarding the risks of combined estrogen/progestin was followed by a substantial decline in the number of women receiving HT therapy, and the latest results are likely to lead to further discontinuations. This trend is likely to increase the incidence of osteoporosis in women who do not receive another form of antiresorptive therapy after discontinuation of HT. Specifically, several studies in postmenopausal women have shown that the rate of bone loss after withdrawal of estrogen therapy is greatly accelerated to early postmenopausal levels, resulting in reductions in BMD of up to 4.5% at the lumbar spine and up to 3.3% at the hip during the first year after therapy discontinuation. Importantly, the rate of hip fracture was 65% higher in women who had discontinued HT during the previous 5 years than in women who never used HT in a longitudinal observational study of more than 140,000 women. Therefore, women discontinuing HT should be screened for osteoporosis and counseled regarding the need for an alternate form of therapy to prevent fracture.

Bisphosphonates

Mechanism of action

Bisphosphonates are analogs of pyrophosphate that bind selectively to bone mineral and are taken up by osteoclasts during the process of bone resorption. Once inside the cell, bisphosphonates inhibit farnesyl dipiphosphate synthase (an enzyme in the cholesterol pathway) that ultimately leads to osteoclast deactivation and apoptosis. Consequently, bone turnover is suppressed, leading to a longer life span for each remodeling unit, which in turn permits more complete secondary mineralization of each resorption pit and increased bone mass. The overall result of this process is improved bone strength and a reduction in fractures.

Efficacy

Several bisphosphonates—alendronate, risedronate, and ibandronate—are approved for the prevention and treatment of osteoporosis on the basis of their established antifracture efficacy in clinical trials. Efficacy data for each of these agents in early postmenopausal women are reviewed below.

Alendronate has demonstrated a reduced risk of vertebral fractures in older postmenopausal women (mean ages: 68-71 years) with and without preexisting vertebral fractures who were enrolled in the Fracture Intervention Trial (FIT). Alendronate also has been shown to reduce bone turnover and to prevent bone loss in several trials in early postmenopausal women. Daily alendronate (10 mg) significantly reduced markers of bone resorption within 3 months of initiation of therapy in a study of women with a mean age of 53 years who were fewer than 2 years postmenopause. The early decreases in bone resorption observed with alendronate treatment are followed by decreased bone formation; a new, reduced steady state of bone turnover is achieved after approximately 6 months of continuous treatment without evidence of impaired mineralization. The effects of alendronate on bone turnover are paralleled...
by sustained or increased BMD. In a study of women 6 to 36 months postmenopause and aged 40 to 59 years, daily treatment with alendronate for 5 years prevented bone loss at the spine, hip, and total body; after discontinuation of therapy, bone loss resumed at the rapid rate typical of early postmenopause.44

In another 2-year study of therapy in women aged under 60 years, daily alendronate (5 mg) significantly increased BMD at the lumbar spine and hip by 3.5% and 1.9%, respectively (P < .001 vs baseline at both sites).42 Importantly, BMD continues to increase at the lumbar spine and hip through 10 years of treatment.65

The fact that these benefits were achieved early in women with and without prior vertebral fractures is substantial within the year after the initial vertebral fracture.72

In early postmenopausal women (6 months-5 years postmenopause) with BMD values within 2 SDs of normal, daily risedronate (5 mg) increased BMD at the lumbar spine by more than 5% versus placebo during 2 years of treatment (P < .05 vs baseline and placebo).43 After discontinuation of treatment, bone turnover increased to pretreatment levels within 6 months, and bone mass declined to below pretreatment levels within 1 year indicating that continuous treatment is needed to maintain this protective effect.43

In women aged 36 to 55 years with artificial menopause caused by chemotherapy, cyclical risedronate therapy delayed the decrease in BMD seen with placebo at both the femoral neck and the lumbar spine. After 2 years, the difference between the 2 groups was 2.6% and 2.5%, respectively. On treatment withdrawal, bone turnover increased and bone mass decreased.73 Both of these studies show that risedronate effectively prevents bone loss in early postmenopausal women and that continuous treatment is needed to maintain this protective effect. Like alendronate, risedronate is available in a once weekly, 35-mg tablet that is therapeutically equivalent to 5 mg given once daily.74,75

Importantly, risedronate has been shown to prevent bone loss and to preserve trabecular architecture in early postmenopausal women (age 52 years).76 By using 3-dimensional microcomputed tomography, Dufresne et al76 analyzed bone biopsy specimens from the iliac crest of risedronate- and placebo-treated patients and found that there was a significant deterioration in trabecular architecture after 1 year of treatment with placebo. In contrast, risedronate prevented the loss in bone mass and preserved trabecular architecture over this same time period (Figure). A recent analysis of pivotal clinical trials with risedronate showed that reductions in vertebral fracture risk with risedronate therapy were independent of increases in BMD values.77 These studies establish that risedronate maintains both bone mass and bone architecture. Together, these effects contribute to the improved bone quality and bone density that helps to prevent osteoporotic fractures.

**Ibandronate** was approved by the Food and Drug Administration for the prevention and treatment of postmenopausal osteoporosis in May 2003, although currently it is not being marketed in the United States.78 Both daily and intermittent administration of ibandronate has demonstrated antifracture activity in late postmenopausal women (mean age: 69 years).79 In a 2-year study of early postmenopausal women (1-3 years since menopause) without osteoporosis, daily ibandronate maintained or increased BMD at the hip and the spine.80 Similarly, the once weekly dosage form of ibandronate produced BMD increases of 5.3% at the spine and 3.5% at the hip versus placebo over 2 years of therapy in early postmenopausal women (1-3 years postmenopause; mean age: 55 years) with osteopenia.81

**Safety and tolerability**

Bisphosphonates are generally well tolerated with an overall incidence of adverse experiences similar to that of placebo.1,80,81 The results of an endoscopy study82 and retrospective analyses using an integrated medical and pharmacy claims database,83,84 showed that treatment with risedronate versus alendronate was associated with significantly fewer gastrointestinal (GI) adverse events, a significantly lower incidence of GI ulcers during the first 14 days of administration, and lower direct medical costs and resource utilization for GI-related adverse events within the first 4 months of treatment. However, data from FIT show that the incidence of upper GI adverse events was similar among once daily alendronate (5 and 10 mg) and placebo, with abdominal pain and dysphagia being the only symptoms significantly increased with alendronate.85 Overall, oral bisphosphonates are very well tolerated.

**Calcitonin**

**Mechanism of action**

Calcitonin, an inhibitor of osteoclast activity, exerts rapid, transient, and reversible inhibition of bone resorption.86
Figure Three-dimensional microcomputed tomography of iliac crest bone biopsy specimens. Reprinted with permission from Dufresne et al.76
Efficacy

Studies of calcitonin in early menopause have yielded consistent results. The studies described below evaluated the efficacy of subcutaneously or intramuscularly injected calcitonin.\textsuperscript{87,88} In the first study, thrice weekly subcutaneous injections of calcitonin prevented vertebral bone loss as effectively as conjugated estrogens over 2 years in a population of women who were generally within 5 years postmenopause.\textsuperscript{87} Another study showed that 2 years of therapy with biweekly intramuscular injections of calcitonin also prevented vertebral bone loss in women 6 months to 10 years postmenopause.\textsuperscript{88} Since study completion, a nasal spray formulation of salmon calcitonin has become available for the treatment of osteoporosis in women more than 5 years postmenopause and is now the preferred dosage form.\textsuperscript{89} In a 5-year study of postmenopausal women with established osteoporosis and prevalent vertebral fractures, calcitonin 200 IU intranasally daily decreased vertebral fractures significantly by 33% compared with placebo. However, these women were, on average, 22 years postmenopausal.\textsuperscript{37} There are no data available on nasal spray calcitonin and early menopausal bone loss.

Tolerability

The tolerability profile of calcitonin nasal spray is similar to that of placebo with the exception of a higher incidence of rhinitis ($P < .01$) and a lower incidence of headache ($P = .03$) with calcitonin than with placebo.\textsuperscript{37}

Selective estrogen receptor modulators

Mechanism of action

Developed to provide the benefits of estrogen therapy without its unwanted side effects, selective estrogen receptor modulators (SERMs) exert estrogen-agonistic effects on the skeleton and lipids and estrogen-antagonistic effects on the uterus and breast.\textsuperscript{90} Through this action, SERMs decrease bone turnover, although less potently than conjugated equine estrogens\textsuperscript{91} and bisphosphonates.\textsuperscript{91-93}

Efficacy

The efficacy of raloxifene was established in the Multiple Outcomes of Raloxifene Evaluation trial in 7705 women with postmenopausal osteoporosis. Over 4 years of therapy, both high and low doses of raloxifene reduced the risk of vertebral fracture (by 43% and 36%, respectively) versus placebo,\textsuperscript{94} with antifracture efficacy observed within the first year of treatment.\textsuperscript{95} However, raloxifene had no effect on the risk of nonvertebral fractures.\textsuperscript{94} Data for raloxifene in early postmenopausal women are limited. In 1 trial, 5 years of therapy with raloxifene significantly increased BMD at the spine (2.8%; $P < .001$ vs placebo) and hip (2.6%; $P < .001$ vs placebo) and reduced markers of bone turnover in women an average of 5 years postmenopause and aged 55 years.\textsuperscript{45} Another study showed that 1 year after discontinuation of long-term (5-year) raloxifene therapy, the rate of bone loss was similar to that in women receiving placebo.\textsuperscript{46}

Tolerability

Adverse events observed with raloxifene include hot flashes, leg cramps, and an increase in the incidence of deep vein thrombosis comparable to that observed with estrogen therapy.\textsuperscript{1,94}

Parathyroid hormone

Mechanism of action

Although the mechanism of action is not completely understood,\textsuperscript{96} parathyroid hormone (PTH) appears to stimulate bone formation on quiescent bone surface that is not simultaneously undergoing remodeling, exerting its actions mainly on trabecular bone surfaces, and to a lesser extent, on some periosteal and endocortical bone surfaces.\textsuperscript{97} Both osteoblast and osteoclast activity is increased with a net increase in bone formation.

Efficacy

In an intervention trial in postmenopausal women ($\geq 5$ years postmenopause), approximately 18 months of treatment with injectable recombinant human PTH (1-34; the N-terminal region of PTH) or teriparatide significantly increased BMD of the lumbar spine by 13.7% and of the total hip by 3.6%, and reduced the risk of vertebral fractures by up to 69% (all comparisons $P < .001$ vs placebo).\textsuperscript{39} No trials have been conducted with teriparatide in early postmenopausal women.

Tolerability

In the trial described previously, dose-related adverse effects included nausea, headache, and hypercalcemia.\textsuperscript{39} Because safety and efficacy data of teriparatide have not been evaluated in patients for more than 2 years, its use is restricted to a period lasting no longer than 2 years. Moreover, treatment is limited to postmenopausal women with severe osteoporosis and at high risk of fracture because teriparatide has been shown to increase the incidence of osteosarcoma in rats.\textsuperscript{98}

Combination regimens

Combination therapy consisting of 2 agents with different mechanisms of action has been explored as a
possible means of inducing greater increases in BMD and greater reductions in fracture risk than would be possible with either agent used alone. The efficacy of combination therapy in early postmenopausal women and its impact on the risk of fracture have not been established.

**Bisphosphonates plus HT**

In a prospective, randomized, double-blind study in postmenopausal women (mean ages: 58–59 years), increases in BMD with risedronate plus HT versus HT alone were slightly but significantly higher at the femoral neck and midshaft radius and similar at the lumbar spine. Combination therapy with alendronate plus HT in postmenopausal women (mean age: 62 years) has been shown to significantly increase BMD at both the spine and hip compared with HT monotherapy.

In each of these studies, combination therapy with a bisphosphonate plus HT showed tolerability comparable to that of HT alone. However, as noted previously, HT is not recommended unless there is a significant risk of osteoporosis and nonestrogen medications are not considered appropriate.

**Antiresorptives and teriparatide**

The combined use of alendronate with teriparatide has not been shown to produce an additive effect on bone density in women with postmenopausal osteoporosis (mean ages: 69-71). Moreover, in men with osteoporosis, prior exposure to alendronate appears to diminish BMD response to teriparatide at selected sites (eg, lumbar spine, femoral neck). Similarly, previous treatment with alendronate in postmenopausal women (mean ages: 69-71) has attenuated the expected increase in BMD at the hip and spine with teriparatide. In contrast, there was no effect of raloxifene on the usual teriparatide-induced increase in BMD. To date, there have been no reports of intervention studies conducted in postmenopausal women.

**Bisphosphonates plus SERMs**

In a multicenter, randomized, double-blind study, therapy with alendronate plus raloxifene was shown to exert independent and additive effects on BMD that were significantly greater than either agent alone, resulting in mean gains of 5.3% at the lumbar spine and 3.7% at the femoral neck over 1 year of therapy. The effect of combination therapy on fracture risk was not assessed in this trial and therefore remains to be established.

**Conclusion**

It is well established that it is never too late to initiate treatment to prevent fractures in postmenopausal women. Similarly, it is never too early in the postmenopause to evaluate women for bone loss and advise them on steps to take to prevent the declines in bone mass and quality that increase the risk of future osteoporosis and fracture. Although all women can benefit from nonpharmacologic modifications to maximize bone mass and reduce the risk and consequences of falling, pharmacologic treatment should be considered for women identified through BMD testing and risk-factor assessment to be at high risk of osteoporotic fracture. Clearly, BMD decreases rapidly in early postmenopause, and certain interventions may prevent bone loss. Both the NOF and ACOG recommend that women with T-scores less than −2.0 and no risk factors, women with T-scores less than −1.5 with at least 1 risk factor, and women with a preexisting hip or vertebral fragility fractures are candidates for pharmacologic intervention. Long-term data attest to the safety and efficacy of several antiresorptive agents as monotherapy.

Strategies to prevent bone loss are clearly preferred to curb the ever-increasing incidence of osteoporosis and related fractures. Early evaluation, education, and appropriate intervention should be considered in all women at the time of menopause. Bone loss in early menopause needs to be further studied to determine long-term fracture risk reduction and appropriate treatment interventions specifically for this age group.

**Acknowledgment**

Dr Delaney would like to thank David K. Schroeder for assistance in the preparation of this manuscript.

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