Prevention and treatment of postmenopausal osteoporosis

Sunna Kwun MD,a Marc J Laufgraben MD MBA FACE FACP,b Geetha Gopalakrishnan MDc,*

aEndocrine Fellow, Division of Endocrinology, Alpert Medical School of Brown University, Hallett Center for Diabetes and Endocrinology, 900 Warren Ave, East Providence, RI 02914, USA
bDivision Head, Division of Endocrinology, Diabetes, and Metabolism, Cooper Medical School of Rowan University, Cooper University Hospital, Cooper Plaza, Suite 220, Camden, NJ 08103, USA
cAssociate Professor of Medicine, Alpert Medical School of Brown University Medicine, 900 Warren Ave, East Providence, RI 02914, USA
*Correspondence: Geetha Gopalakrishnan. Email: ggopala@lifespan.org

Key content
• Osteoporotic fractures are associated with increased morbidity and mortality.
• Clinical history and bone densitometry can identify individuals at risk for osteoporotic fractures.
• Treatment is available to prevent and treat osteoporosis.

Learning objectives
• Make the diagnosis of osteoporosis.
• Decide appropriate treatment for the prevention or treatment of osteoporosis.

Ethical issues
• Maximising health benefit while minimising financial implications.

Key words: menopause / osteoporosis / bone density / calcium / vitamin D / bisphosphonates

Introduction
Osteoporosis is the most common skeletal disorder affecting postmenopausal women. It is characterised by a decrease in bone mass resulting in fragility fractures. It is estimated that one-third of adult women will have an osteoporosis-related fracture in their lifetime.1 Osteoporosis-related fractures typically involve the spine, hip, humerus and forearm. Colles’ (forearm) fractures are more common in younger postmenopausal women while hip fractures peak in the seventh to eighth decade of life.2

Most vertebral fractures are asymptomatic. However, they can cause back pain, height loss and kyphosis. Vertebral deformities may result in decreased lung capacity, impaired balance and gastrointestinal symptoms.2 The consequences of a hip fracture are often debilitating. It is estimated that 50% of patients with a hip fracture will no longer be able to live independently and 20% will die in the year following the fracture.1 Therefore, various organisations have recommended screening strategies to identify those at high risk of osteoporotic fractures.1,3–5

Risk factor assessments and bone mineral density (BMD) measurements can identify patients at risk of osteoporotic fractures. A decrease in bone density is associated with an increased risk of fractures. In general, bone mass increases during childhood and adolescence to reach a peak level by the third decade of life. Subsequently, a steady rate of decline is noted with age in both sexes. In women, the decline of estrogen at menopause leads to increased bone resorption and a rapid decline in bone density in the early postmenopausal years.6,7 Furthermore, certain lifestyle factors, medical conditions and medications can also impact peak bone mass, rate of bone loss and fracture risk. Since pharmacological treatments can substantially reduce fracture rates, identifying high-risk individuals is the cornerstone of osteoporosis management.

Susceptible populations
The presence of one or more risk factors increases the risk of osteoporosis (Box 1). Modification of these factors can reduce fracture rates. Therefore, osteoporosis risk assessment is recommended in all postmenopausal women. Bone density screening can identify individuals at risk for osteoporotic fractures. Independent of bone density, risk factors for an osteoporosis-related fracture include: age, female gender, current smoking, high alcohol intake (>3 units/day), history of hip fracture in a parent, prior fragility fracture, low body mass index, rheumatoid arthritis and use of glucocorticoids (prednisolone >5 mg for more than 3 months).8
Box 1. Risk factors for osteoporosis and fractures

<table>
<thead>
<tr>
<th>General</th>
<th>Female gender, older age, Caucasian race</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractures</td>
<td>Previous fragility fracture</td>
</tr>
<tr>
<td>Family history</td>
<td>Heredity is the greatest influence on peak bone mass: history of fracture in a first-degree relative can double fracture risk</td>
</tr>
<tr>
<td>Body habitus</td>
<td>Low weight (commonly approximated as &lt;57 kg), recent weight loss of 4.5 kg or more, kyphosis</td>
</tr>
<tr>
<td>Hormones</td>
<td>Delayed menarche (&gt;15 years of age), early menopause (estrogen deficiency before 45 years), other causes of hypoestrogenism</td>
</tr>
<tr>
<td>Lifestyle factors</td>
<td>Cigarette smoking, poor nutrition, heavy alcohol consumption (3 or more units of alcohol per day), insufficient physical activity</td>
</tr>
<tr>
<td>Risk factors for falls</td>
<td>Inadequate lighting, loose rugs, poor vision, orthostatic hypotension, weak muscles, problems with balance</td>
</tr>
<tr>
<td>Underlying medical issues</td>
<td>Rheumatoid arthritis, chronic renal disease, organ transplantation, hyperparathyroidism, Cushing’s syndrome, hyperthyroidism, malabsorption, multiple myeloma, HIV, type 1 diabetes</td>
</tr>
<tr>
<td>Medications</td>
<td>Chemotherapeutic drugs, aromatase inhibitors, gonadotrophin-releasing hormone agonists, depo-medroxyprogesterone contraceptives, antiepileptic drugs, glucocorticoids, lithium</td>
</tr>
</tbody>
</table>

Options for bone density screening

Central dual-energy X-ray absorptiometry (DXA) is the standard method used to evaluate BMD of the spine, hip and forearm. The resulting BMD correlates with bone strength and predicts fracture risk. Therefore, DXA can be used to diagnose osteoporosis and to monitor patients on or off therapy.

Alternative screening tools, such as computed tomography-based absorptiometry, peripheral DXA and ultrasonography are not routinely recommended to diagnose osteoporosis or to monitor changes in bone density.

Recommendations for screening

Osteoporosis risk factors should be assessed in all postmenopausal women. The National Osteoporosis Guideline Group recommends using the FRAX® (Fracture Risk Assessment) calculator (available online at www.shef.ac.uk/FRAX) to identify individuals at sufficient risk for fracture to warrant treatment or further evaluation by DXA. Using clinical risk factors, an individual’s 10-year risk of major osteoporosis-related fracture is estimated. Depending on the patient’s age, body mass index and fracture probability, a recommendation is made to reassure the patient without further evaluation, pursue DXA for further refinement of fracture risk, or, in some cases, begin pharmacological therapy without DXA testing.

In contrast, US guidelines recommend DXA for all women 65 or older, or for younger postmenopausal women with major osteoporotic fracture risk greater than 9.3% by FRAX®.

Generally, bone density testing is not recommended in healthy premenopausal women. However, adult women with certain medical conditions such as a history of fragility fractures, rheumatoid arthritis or glucocorticoid treatment can be considered for bone density testing. Testing should also be considered for women with premature ovarian insufficiency who are not using estrogen.

Interpreting DXA results

DXA reports usually include assessment of the hip (total hip and femoral neck), lumbar spine or both. The National Osteoporosis Guideline Group (NOGG) recommends assessment of a single site with emphasis on the femoral neck, particularly in older people. A forearm BMD may be useful in patients with hyperparathyroidism. The BMD result is then compared with the mean BMD of a normal, young, gender-matched adult population (T-score) and to the mean BMD of an age, race and gender-matched population (Z-score). Osteoporosis is defined by a T-score <–2.5 standard deviation (Box 2). In postmenopausal women, the Z-score may used to characterise BMD well outside the expected range for age, race and gender (Box 3), often indicating an individual with higher risk for secondary causes of osteoporosis.

Box 2. World Health Organization (WHO) bone mineral density (BMD) diagnostic criteria

<table>
<thead>
<tr>
<th>Bone density category</th>
<th>WHO BMD diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>T-score ≥ –1</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>T score &lt; –1 but &gt; –2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>T score ≤ –2.5</td>
</tr>
</tbody>
</table>

Established osteoporosis denotes patients who meet BMD criteria for diagnosis who have already experienced fragility fracture.

Box 3. International Society for Clinical Densitometry (ISCD) bone density diagnostic criteria

<table>
<thead>
<tr>
<th>Bone density category</th>
<th>ISCD diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within the expected range for age</td>
<td>Z-score &gt; –2.0</td>
</tr>
<tr>
<td>Below the expected range for age</td>
<td>Z-score ≤ –2.0</td>
</tr>
</tbody>
</table>
Laboratory assessments

The NOGG recommends the following in all people with osteoporosis: complete blood count, sedimentation rate, serum calcium, albumin, creatinine, phosphate, liver enzymes and thyroid function tests. Other guidance recommends routine measurement of 25-hydroxy vitamin D and 24-hour urinary calcium excretion. Tests such as serum protein electrophoresis, 24-hour urine free cortisol, tissue transglutaminase antibody and intact parathyroid hormone (PTH) can also be considered if clinically indicated.

Bone turnover markers such as urinary N-telopeptide have limited use in monitoring therapy. In large clinical trials suppression of bone turnover markers was noted after 3–6 months. When testing, a second urine collection in the early morning after an overnight fast, is recommended.

General recommendations

Lifestyle changes

Therapeutic lifestyle changes should focus not only on improving bone density but also on falls prevention. Nearly 30% of older adults fall each year and 5% of these falls result in fractures or hospitalisation. Therefore, alleviating home hazards, modifying psychotropic medications, correcting vision and hearing impairment, and addressing neurological deficits can reduce falls and prevent fractures. Furthermore, regular physical activity improves agility, strength, posture and balance, and thus reduces falls. Although the optimal exercise is unknown, weight-bearing exercises have been shown to improve bone density and reduce fracture rates. Immobilisation, on the other hand, precipitates bone loss and therefore should be avoided whenever possible.

Women should be advised to avoid smoking and restrict alcohol intake to no more than 2 units per day. Smokers have low bone mass and lose bone more rapidly than non-smokers. Excessive alcohol intake can affect nutrition as well as balance, leading to low bone density, falls and fractures. Hip protectors can reduce the impact of a fall and therefore may reduce hip fracture in older nursing home patients.

Calcium and vitamin D

Adequate intake of calcium and vitamin D is recommended for all postmenopausal women. The NOGG recommends at least 1000 mg calcium daily. Dietary intake of calcium should be emphasised in light of recent data suggesting a possible increase in cardiovascular events with calcium supplementation.

Box 4. Calcium-rich foods

<table>
<thead>
<tr>
<th>Dairy products</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoghurt</td>
<td>Cheese</td>
<td>Milk</td>
</tr>
<tr>
<td>Fish</td>
<td>Salmon</td>
<td>Sardines</td>
</tr>
<tr>
<td>Nuts</td>
<td>Almonds</td>
<td>Walnuts</td>
</tr>
<tr>
<td>Fruit</td>
<td>Figs</td>
<td>Oranges</td>
</tr>
<tr>
<td>Vegetables</td>
<td>Broccoli</td>
<td>Spinach</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Calcium-fortified foods</td>
<td>Tofu</td>
</tr>
</tbody>
</table>

Estimating calcium intake: Total calcium intake + 250 mg from a general non-dairy diet = total daily calcium intake. Note: 1 serving of dairy = ~300 mg calcium

Vitamin D is necessary for calcium absorption and bone health. Vitamin D can be formed by exposure of the skin to UV rays from the sun; however, formation is decreased by age, geographic location away from the equator, sunscreen, darker skin tones, time of day and season. Thus, most women will depend on dietary intake and supplements to maintain adequate levels. A vitamin D intake of 800 IU daily is recommended for all postmenopausal women. If serum 25-hydroxyvitamin D concentration is measured, most experts recommend a goal of at least 75 nmol/L.

Pharmacological treatment options

Pharmacological therapy is recommended for postmenopausal women who have a history of fragility fracture or who meet NOGG-designated thresholds for treatment based on FRAX. NOGG emphasises that the threshold for diagnosing osteoporosis may be different from the threshold for pharmacological treatment of osteoporosis. Furthermore, it is important to keep in mind that the FRAX tool should not be used in premenopausal women, women under 40 years or on pharmacological therapy.
By contrast, US guidelines suggest treatment of all postmenopausal women with fragility fracture or T-score at any site <−2.5. For US patients with osteopenia, FRAX® is used to identify patients with sufficient fracture risk to merit preventive treatment. It is important to identify these patients since a majority of osteoporotic fractures occur in patients with T-scores better than −2.5. Pharmacological therapy is recommended in patients with osteopenia if the 10-year risk of a hip fracture is greater than 3% or major osteoporosis-related fracture risk is greater than 20%.5

Antiresorptive agents
Bisphosphonates inhibit osteoclast-mediated bone resorption. By slowing the bone remodelling cycle, bisphosphonates increase BMD in postmenopausal women and reduce the risk of osteoporotic fractures. Although all bisphosphonates approved for osteoporosis treatment have been shown to reduce vertebral fractures, only certain agents, such as alendronate, risedronate and zoledronic acid, reduce the rate of hip fractures (Table 1). Furthermore, the acquisition costs of these agents can vary. In general, alendronate is fairly inexpensive and is the preferred agent for postmenopausal osteoporosis.21–25

In clinical trials, BMD remains stable or decreases slowly after discontinuation of bisphosphonates. Although long-term fracture benefit is unknown, fracture protection seems to persist for up to 5 years after drug discontinuation in low-risk patients treated with bisphosphonates for 5 years. Therefore, a drug holiday can be considered after 5 years of treatment in some patients. The drug can be restarted if there is evidence of bone loss on serial BMD measurements.

The most common side effect of bisphosphonates is oesophageal irritation. Therefore, individuals with oesophageal abnormalities who delay oesophageal emptying and those who cannot stand or sit upright for at least 30 to 60 minutes after dosing should not receive bisphosphonates. Additionally, women with hypocalcaemia and those with glomerular filtration rate lower than 30–35 ml/min should not receive bisphosphonates.1,3

Bisphosphonates are poorly absorbed from the gastrointestinal tract, so for maximal absorption they must be taken on an empty stomach with water, with no further oral intake for 30 to 60 minutes. Parenteral bisphosphonates are generally reserved for those with documented oesophageal disorders or gastrointestinal intolerance to bisphosphonates. Rarely, transient flu-like illness can occur with oral or intravenously administered bisphosphonates. This is considered an acute phase reaction that can be treated symptomatically.1,3

There is a theoretical concern regarding oversuppression of bone turnover with long-term bisphosphonate use. Several hundred case reports of atypical hip fractures involving the subtrochanteric region have been reported in patients treated with long-term bisphosphonates, that is, for more than 3 years. In addition, osteonecrosis of the jaw (ONJ) has been observed in patients receiving bisphosphonates. While the vast majority of ONJ cases have occurred in cancer patients receiving intravenous bisphosphonates, there have been some cases of ONJ occurring in patients with osteoporosis taking oral bisphosphonates.28 Incidence of both phenomena is unknown and there are no data to support discontinuation of bisphosphonate treatment based on the theoretical risk.

Strontium ranelate decreases bone resorption and maintains bone formation. Although the mechanism of action is unknown, it reduces the risk of both vertebral and hip fractures. It has been approved for the treatment of postmenopausal osteoporosis in the UK but not in the USA. It is administered orally at least 2 hours after a meal. It is not recommended in individuals with renal impairment and should be used with caution in patients at risk of venous thromboembolism. Other side effects include hypersensitivity reaction, diarrhoea, headache and dermatitis.1

Nasal calcitonin is approved for treatment of postmenopausal osteoporosis. It inhibits osteoclastic bone resorption but is less effective than other pharmacological therapies. It has been shown to reduce the risk of vertebral fractures but not non-vertebral or hip fractures in postmenopausal women. Calcitonin is generally reserved as an alternative for women who cannot take other osteoporosis agents. Side effects include rhinitis and nasal discomfort. It is contraindicated in patients with hypocalcaemia and nasal ulcerations.1,3

Denosumab inhibits bone resorption by interfering with the proliferation and differentiation of osteoclasts. Denosumab is a monoclonal antibody directed to RANKL.

### Table 1. Bisphosphonates associated with a reduction in hip and vertebral fractures

<table>
<thead>
<tr>
<th>Bisphosphonate</th>
<th>Decrease in hip fractures</th>
<th>Decrease in vertebral fractures</th>
<th>Oral formulation</th>
<th>IV formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Etidronate</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risedronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
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</tbody>
</table>

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(receptor activator of nuclear factor-kappa B ligand) receptor. In contrast to bisphosphonates, denosumab may be used in women with renal insufficiency. In postmenopausal women with osteoporosis, denosumab reduces vertebral, non-vertebral and hip fractures. Adverse side effects include increased incidence of skin infections, osteonecrosis of the jaw and hypocalcaemia.1,3

Hormone therapies
Estrogen slows bone resorption, improves bone density and reduces hip and vertebral fractures. However, the benefits of estrogen dissipate quickly after drug discontinuation.1,3 Estrogen replacement therapy in older postmenopausal women is associated with multiple nonskeletal risks including venous thromboembolism, breast cancer, cardiovascular events and dementia.29 Since there are alternative treatment options for osteoporosis, the primary indication for systemic hormonal therapy is limited to individuals with moderate-to-severe menopausal symptoms. However, in women with premature ovarian failure or early menopause, estrogen replacement therapy should be considered for bone and other health benefits.30

Raloxifene is a selective estrogen receptor modulator that inhibits bone resorption. It has been shown to improve bone mineral density and reduced vertebral fractures.1,31 However, a reduction in non-vertebral or hip fractures has not been adequately evaluated.1 Side effects include venous thromboembolism, vasomotor symptoms and leg cramps.1,3

Anabolic therapy
Two PTH peptides – teriparatide (recombinant human PTH 1–34) and recombinant human PTH (1–84) – are approved for use in the UK. PTH peptides stimulate bone formation by osteoblasts. Teriparatide has been shown to reduce vertebral and non-vertebral fractures but not hip fractures, while recombinant human PTH (1–84) has only been shown to reduce vertebral fractures. Treatment duration is limited to 24 months. These agents are contraindicated in patients with hypercalcaemia, renal or liver impairment, skeletal radiation exposure, malignancy involving the bone and other metabolic bone disease.1,3

Treatment considerations
Cost-effectiveness analysis guides treatment strategies recommended by various organisations in both the US and UK. The choice of agent is determined by anti-fracture data, side effect profile and acquisition costs. Alendronate is used for firstline treatment of osteoporosis in most postmenopausal women. Other bisphosphonates can be considered in patients who cannot tolerate alendronate. Estrogen replacement therapy can be prescribed to younger postmenopausal women with menopausal symptoms. Strontium ranelate, denosumab and raloxifene are options for bisphosphonate-intolerant patients who have a high risk of fracture based on age, BMD and clinical risk factors. Because of the high cost of therapy, teriparatide is reserved for very high-risk patients who are intolerant of other agents or who have had an unsatisfactory response to initial treatment, that is, fragility fracture and declining BMD while adherent to therapy.1,3,21–25

Conclusions
Prevention of osteoporotic fractures is a major public health issue, which will continue to grow in importance as the population ages. Attention to appropriate screening by FRAX®, selective use of DXA, and treatment decisions based on age and fracture risk will help to maximise the cost–benefit ratio of osteoporosis prevention and treatment.

Conflict of interest
None declared.

References
5 International Osteoporosis Foundation [www.iofbonehealth.org/].
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