Postmenopausal Osteoporosis
A Major Public Health Problem

- Osteoporosis is a major public health problem. More than 10 million Americans have osteoporosis, and an additional 43 million have low bone mass, according to data from the U.S. National Health and Nutrition Examination Survey.

- More than 2 million osteoporosis-related fractures occur each year in the United States, and more than 70% of these occur in women.

- More than 20% of postmenopausal women have prevalent vertebral fractures. As the most common osteoporotic fracture, vertebral fractures are a hallmark of the disease and indicate a high risk for future fractures. They are also associated with impaired pulmonary function and increased mortality risk, especially respiratory deaths. However, the majority of vertebral fractures (2/3) are asymptomatic.


Prevalence of Osteoporosis Increases With Age

• Age is an independent risk factor for osteoporotic fractures. The risk increases progressively with age, doubling every 5 to 10 years. Nearly one-quarter (24.8%) of women 65 and older have osteoporosis. For women 80 and older, that figure rises to more than one-third (35.6%), according to a report from the CDC.

• In addition, more than half (52.3%) of women 65 and older have low bone mass (osteopenia). Although fracture risk is highest in women with osteoporosis, most women who experience a fracture have osteopenia, because there are many more women in this category.
Most Women with Osteoporosis Are Not Treated

- Postmenopausal osteoporosis is preventable and treatable, but only a small proportion of women at increased risk for fracture are evaluated and treated.
- Even among women with fractures, lack of treatment is common. Fewer than 1 in 4 women age 67 or older with an osteoporosis-related fracture undergoes bone density measurement or begins osteoporosis treatment.


Diagnosing Osteoporosis

- Postmenopausal osteoporosis can be diagnosed based on the World Health Organization (WHO) definition: a bone mineral density (BMD) T-score of -2.5 or below in the lumbar spine, femoral neck, total hip, and/or 33% (one-third) radius.

| World Health Organization Criteria for Classification of Osteopenia and Osteoporosis |
|----------------------------------|--------------------|
| Category                          | T-score            |
| Normal                            | -1.0 or above      |
| Low bone mass (osteopenia)*       | Between -1.0 and -2.5 |
| Osteoporosis                      | -2.5 or below      |

* Fracture rates within this category vary widely. The category of “osteopenia” is useful for epidemiology studies and clinical research but is problematic when applied to individual patients and must be combined with clinical information to make treatment decisions.

Note: this is table 4 from the AACE Guidelines.


Additional Diagnostic Criteria

• In addition to the WHO bone mineral density criteria, these may also be used to diagnose osteoporosis:
  • Low-trauma spine or hip fracture, *regardless* of BMD
  • Osteopenia or low bone mass (T-score between –1 and –2.5) *with* a fragility fracture of proximal humerus, pelvis, or possibly distal forearm
  • Low bone mass or osteopenia and high FRAX® (*Fracture Risk Assessment Tool*) fracture probability based on country-specific thresholds

The Fracture Risk Assessment Calculator

- The FRAX calculator is available online from the University of Sheffield, UK

The calculation tool includes a questionnaire with various factors to consider for calculating the ten-year probability of fracture with BMD. It also includes weight and height conversion tools.

For USA use only:
Consider FDA-approved medical therapies in postmenopausal women and men aged 50 years and older, based on the following:

- A hip or vertebral (clinical or morphometric) fracture
- T-score ≤ -2.5 at the femoral neck or spine after appropriate evaluation to exclude secondary causes
- Low bone mass (T-score between -1.0 and -2.5 at the femoral neck or spine) and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted WHO algorithm
- Clinicians judgment and/or patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels
Screening for Postmenopausal Osteoporosis

- All postmenopausal women age 50 or older should undergo clinical assessment for osteoporosis and fracture risk, including a detailed history and physical examination. Tools such as FRAX should be used when available.

- BMD testing is the gold standard in diagnosing osteoporosis. However, this test is not always available. The decision to measure BMD should be based on an individual’s clinical fracture risk profile and skeletal health assessment.

Screening Recommendations

• Both the AACE and the U.S. Preventive Services Task Force recommend BMD testing for all women aged 65 and older as well as younger postmenopausal women at increased risk for bone loss and fracture based on fracture risk analysis.

• BMD measurement is not recommended in children, adolescents, healthy young men, or premenopausal women, unless there is a significant fracture history or there are specific risk factors for bone loss.


Clinical Presentation

• Fracture is the single most important manifestation of postmenopausal osteoporosis. Osteoporotic fractures are usually caused by low-energy injuries such as a fall from standing height.

• Vertebral fractures, however, may occur during routine daily activities, without a specific fall or injury. In clinical practice, it may be difficult or impossible to reconstruct the mechanical force applied to bone in a particular fall.

Clinical Presentation

• Osteoporosis-related fractures can lead to pain, disability, and deformity. They reduce quality and quantity of life.

• Hip fractures are the most serious consequence of postmenopausal osteoporosis. Women with hip fracture have an increased mortality of 12% to 20% during the subsequent two years. More than 50% of hip fracture survivors are unable to return to independent living. Many survivors require long-term nursing home care.

• Other low-trauma, osteoporosis-related fractures include those of the proximal humerus, pelvis, and in some cases the distal forearm.


### Treatment

- To identify coexisting medical conditions that cause or contribute to bone loss, an appropriate medical evaluation is indicated for all women with postmenopausal osteoporosis. Some causes of secondary osteoporosis include the following.

<table>
<thead>
<tr>
<th>Endocrine or metabolic causes</th>
<th>Nutritional/GI conditions</th>
<th>Drugs</th>
<th>Disorders of collagen metabolism</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acromegaly</td>
<td>Alcoholism</td>
<td>Antiepileptic drugs</td>
<td>Ehlers-Danlos syndrome</td>
<td>AIDS/HIVa</td>
</tr>
<tr>
<td>Diabetes mellitus Type 1</td>
<td>Anorexia nervosa</td>
<td>Aromatase inhibitors</td>
<td>Homocystinuria due to cystathionine deficiency</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Type 2</td>
<td>Calcium deficiency</td>
<td>Chemotherapy/immunosuppressants</td>
<td>Marfan syndrome</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>Chronic liver disease</td>
<td>Depo-Provera</td>
<td>Osteogenesis imperfecta</td>
<td>Gaucher disease</td>
</tr>
<tr>
<td>Hypercortisolism</td>
<td>Malabsorption syndromes/malnutrition</td>
<td>Glucocorticoids</td>
<td></td>
<td>Hemophilia</td>
</tr>
<tr>
<td>Hyperparathyroidism</td>
<td>(including celiac disease, cystic fibrosis, Crohn's disease, and gastric resection or bypass)</td>
<td>Gonadotropin-releasing hormone agents</td>
<td></td>
<td>Hypercalciuria</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Total parenteral nutrition</td>
<td>Heparin</td>
<td></td>
<td>Immobolization</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>Vitamin D deficiency</td>
<td>Lithium</td>
<td></td>
<td>Major depression</td>
</tr>
<tr>
<td>Hypophosphatasia</td>
<td></td>
<td>Proton pump inhibitors</td>
<td></td>
<td>Myeloma and some cancers</td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
<td>Selective serotonin reuptake inhibitors</td>
<td></td>
<td>Organ transplantation</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td>Thiazolidinediones</td>
<td></td>
<td>Renal insufficiency/failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thyroid hormone (in supraphysiologic doses)</td>
<td></td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systemic mastocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thalassemia</td>
</tr>
</tbody>
</table>

*Note: This is table 11 from the AACE guidelines.*


Treatment

• Because causes of secondary osteoporosis are common even in apparently healthy, postmenopausal women, laboratory testing should be considered for all women with osteoporosis. Laboratory evaluation could include:
  • Complete blood cell count (CBC)
  • Comprehensive metabolic panel (includes calcium, albumin, and creatinine tests)
  • Serum 25-hydroxyvitamin D
  • Phosphate
  • 24-hour urine collection for calcium, sodium, and creatinine.

Treatment

- If medical history, physical findings, or laboratory test results suggest causes of secondary osteoporosis, additional laboratory evaluation is warranted and may include, but is not limited to, the following.
  - Serum intact parathyroid hormone (PTH) concentration for possible primary or secondary hyperparathyroidism
  - Serum thyrotropin
  - Tissue transglutaminase antibodies for suspected celiac disease
  - Serum protein electrophoresis and free kappa and lambda light chains for suspected myeloma
  - Urinary free cortisol or other tests for suspected adrenal hypersecretion
  - Serum tryptase, urine N-methylhistidine, or other tests for mastocytosis
  - Bone marrow aspiration and biopsy to look for marrow-based diseases
  - Undecalcified iliac crest bone biopsy with double tetracycline labeling (recommended for patients with bone disease and renal failure to establish the correct diagnosis and direct management)
  - Genetic testing for unusual features that suggest rare metabolic bone diseases


Note: This is taken from table 12 in the AACE guidelines.
Treatment

- Lifestyle modifications may improve musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures. These include:
- An adequate intake of calcium and vitamin D
  - Daily supplementation with vitamin D$_3$ at a dose of 1,000 to 2,000 IU is typically needed to maintain an optimal serum 25(OH)D level.
  - For adults age 50 and older, the recommended calcium intake (dietary plus supplements if necessary) is 1,200 mg/day.
- Lifelong participation in regular, weight-bearing, resistance exercise
- Balance-improving exercises to minimize falls
- Avoiding tobacco and excessive use of alcohol
- Eliminating potential risk factors for falling.


Treatment

• The AACE strongly recommends pharmacologic therapy for the following patients:
  • Those with osteopenia or low bone mass and a history of fragility fracture of the hip or spine.
  • Those with a T-score of –2.5 or lower in the spine, femoral neck, total hip, or 33% radius.
  • Those with a T-score between –1.0 and –2.5 in the spine, femoral neck, total hip, or 33% radius, if the FRAX® 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% (in the U.S.) or above the country-specific threshold in other countries or regions.


Treatment

A number of agents are approved by the U.S. Food and Drug Administration for prevention and/or treatment of postmenopausal osteoporosis. Full prescribing information should be reviewed before recommending any specific agent.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax)</td>
<td>5 mg PO daily</td>
<td>10 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>35 mg PO weekly</td>
<td>70 mg PO weeklyb</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70 mg + Dc</td>
</tr>
<tr>
<td>Calcitonin (Miacalcin, Fortical)</td>
<td>—</td>
<td>200 IU intranasally once daily, or 100 IU SQ qod</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td>—</td>
<td>60 mg SQ every 6 mo</td>
</tr>
<tr>
<td>Estrogen (multiple formulations)</td>
<td>Multiple regimens</td>
<td>—</td>
</tr>
<tr>
<td>Ibandronate (Boniva, generic form)</td>
<td>2.5 mg PO daily</td>
<td>2.5 mg PO daily</td>
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<tr>
<td></td>
<td>150 mg PO monthly</td>
<td>150 mg PO monthly</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg IV every 3 mo</td>
</tr>
<tr>
<td>Raloxifene (Evista)</td>
<td>60 mg PO daily</td>
<td>60 mg PO daily</td>
</tr>
<tr>
<td>Risedronate (Actonel, Atelvia, generic form)</td>
<td>5 mg PO daily</td>
<td>5 mg PO daily</td>
</tr>
<tr>
<td></td>
<td>35 mg PO weekly</td>
<td>150 mg PO monthly</td>
</tr>
<tr>
<td></td>
<td>150 mg PO monthly</td>
<td></td>
</tr>
<tr>
<td>Abaloparatide (Tymlos)</td>
<td>—</td>
<td>80 mcg subcutaneously daily</td>
</tr>
<tr>
<td>Teriparatide (Forteo)</td>
<td>—</td>
<td>20 μg SQ daily</td>
</tr>
<tr>
<td>Zoledronic acid (Reclast, generic infusion form)</td>
<td>5 mg IV every 2nd y</td>
<td>5 mg IV once yearly</td>
</tr>
</tbody>
</table>


There are no-head-to-head trials comparing the efficacy of approved drugs. However, four agents (alendronate, risedronate, zoledronic acid, and denosumab) have evidence for broad anti-fracture efficacy (spine, hip, and non-vertebral fracture risk reduction). These should be considered as initial options for most patients who are candidates for pharmacologic therapy.

Treatment

• Patients who have lower or moderate fracture risk can be started on oral agents.
• Injectable agents such as teriparatide, **abaloparatide**, denosumab, or zoledronic acid can be considered as initial therapy for those who have the highest fracture risk.
Treatment

• For patients at high risk of spine fracture but not at risk for hip or non-vertebral fractures, ibandronate and raloxifene may be appropriate. Raloxifene has the additional benefit of reducing breast cancer risk.

• Denosumab is the agent of choice for patients with renal insufficiency. The AACE cautions against using in dialysis patients and those with stage 5 kidney disease due to risk of hypocalcemia.

Sequential Therapy: Follow Anabolic Therapy with Antiresorptive Agents

- Treatment with anabolic agents (teriparatide, abaloparatide) should always be followed by antiresorptive therapy to prevent bone density decline and loss of fracture efficacy. The rationale for using an antiresorptive agent after anabolic therapy is based on both the limited period that anabolic therapy is used and on data showing that bone mineral density declines if antiresorptive therapy is not initiated.


Combination Therapy: Under Investigation

- Combination therapies for osteoporosis are being evaluated, but there are as yet no studies showing that treatment with two or more osteoporosis drugs has a greater effect on fracture reduction than treatment with a single agent.

- Studies of bisphosphonate/PTH analog combinations suggest they do not provide substantial clinical benefit compared with monotherapy. The most promising combination studied to date is teriparatide and denosumab. The DATA study showed that bone mineral density at the spine and hip increased significantly more in postmenopausal women on this combination compared to either drug alone.


Leder BZ et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (the DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab* 2014; 99:1694–700.

Combination Therapy: AACE Recommendation

• Combination therapy substantially raises the cost and probably increases the potential for side effects. Until the effect of combination therapy on fracture risk is better understood, the AACE does not recommend combination therapy for prevention or treatment of postmenopausal osteoporosis.

• However, in certain situations when the patient needs a stronger agent because fracture risk is especially high or there is demonstrated suboptimal effect from raloxifene or hormone replacement therapy (i.e., recurrent fractures, high bone resorption markers, or progression of BMD loss), yet the patient has specific non-bone reasons to continue with these agents, another antiresorptive agent or anabolic therapy could be added to the therapy.


Leder BZ et al. Two years of denosumab and teriparatide administration in postmenopausal women with osteoporosis (the DATA Extension Study): a randomized controlled trial. J Clin Endocrinol Metab 2014; 99:1694–700.

Discontinuation of Denosumab: Clinical Considerations

• Denosumab is a fast-acting and potent antiresorptive agent. However, its effects are rapidly reversible. When denosumab is discontinued, bone turnover rates increase to levels above pretreatment baseline.

• Clinicians should be aware that this post-denosumab “rebound” has been linked to an increased risk of compound vertebral fractures. In addition, evidence suggests that switching from denosumab to teriparatide in particular can lead to bone loss in postmenopausal women.

Treatment

- The AACE has developed the following treatment algorithm as part of its 2016 clinical practice guidelines.

![AACE/ACE 2016 Postmenopausal Osteoporosis Treatment Algorithm](image)