Postmenopausal osteoporosis: prevention and treatment

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Outlines: Osteoporosis

• Impact and overview
• Risk assessment
• Diagnosis assessment
• Management
  – Universal recommendations
  – Pharmacologic treatment

Based on the National Osteoporosis Foundation (NOF)
  Recommendation in 2014
Most common bone disease and major public health problem

Impact and overview

- Osteoporosis affects many patients, of both genders and all races, esp. in the elderly.
- Many patients with osteoporosis-related fractures are not being diagnosed and not receiving the effective therapies.
Basic pathophysiology

- Osteoporosis characterized by **low bone mass**, **deterioration of bone** and **disruption of bone architecture**
- It compromised **bone strength and increase risk of fracture**

Bone with osteoporosis

![Normal Bone](image1.png) ![Osteoporosis Bone](image2.png)

Micrographs of normal vs osteoporotic bone:

: change within cancellous bone as a consequence of bone loss

- Peak bone mass:
  - age 18-25 years
  - determined by genetic factors, nutrition, endocrine status, physical activity and health during growth

- Bone remodeling:
  - a process to maintain healthy bone
  - by balance between older bone removal and new bone replacement

- Bone mass in older adults = peak bone mass – amount of bone subsequently lost
Bone Remodeling

1. RESTING PHASE: A bone surface is covered by a protective layer of bone cells - called lining cells.

2. RESORPTION: During resorption, osteoclasts invade the bone surface and erode it, dissolving the mineral and the matrix.

3. RESORPTION COMPLETE: A small cavity is created in the bone surface - resorption is complete.

4. FORMATION-REPAIR: Bone forming cells called osteoblasts begin to fill in the cavity with new bone.

5. REPAIR COMPLETE: Finally, the bone surface is completely restored.

Bone Remodeling

Fig.1. Complement component 3a (C3a) and collagen triple helix repeat containing 1 (Cthrc1) in the communication between osteoclasts (OC) and osteoblasts (OB). Bone marrow macrophages (BMM) become committed preOC and then mature, multinucleated OC (mOC). C3a is derived from mOC and acts on bone marrow stromal cells (BMSC) to stimulation osteoblastogenesis. Cthrc1 is secreted from mature active OC (maOC) in the middle of bone resorption and stimulates OB differentiation as well as recruitment of BMSC or mesenchymal stem cells (MSC) to resorption lacunae.

J Bone Metab 2014;21:183-187
Pathogenesis of osteoporosis-related fractures

- Aging
- Hypogonadism and menopause
- Clinical risk factors
- High bone turnover
- Inadequate peak bone mass
- Increased bone loss
- Propensity to fall
- Fall mechanics
- Low bone density
- Impaired bone quality
- Falls
- Certain activities
- Excessive bone loading
- Skeletal Fragility
- Fracture

Approach to the diagnosis/management

- Establish the patient’s fracture risk by
  - Detailed history
  - Physical examination
  - BMD assessment
  - Vertebral imaging
  - WHO 10-year estimated fracture probability (FRAX tool)
Risk assessment

• **All postmenopausal women and men age ≥ 50** should be evaluated for osteoporosis risk, need for BMD testing and/or vertebral imaging

• **Many factors** have been associated with an increase risk of osteoporosis-related fracture

• Osteoporosis-related fracture result from falls, so it’s important to evaluate risk factors for falling

• **Measure height annually**, preferably with a wall-mounted stadiometer.

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**Conditions that cause/contribute to osteoporosis**

<table>
<thead>
<tr>
<th>Lifestyle factors</th>
<th>Evaluation for secondary causes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol abuse</td>
<td>Any adulthood fracture</td>
</tr>
<tr>
<td>Frequent falling</td>
<td>Recent, multiple fractures with very low BMD</td>
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<tr>
<td>Inadequate physical activity</td>
<td>Any clinical suggested</td>
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<table>
<thead>
<tr>
<th>Hypogonadal states</th>
<th>Endocrine disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen insensitivity</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Cushing’s syndrome</td>
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<tr>
<td>Panhypopituitarism</td>
<td>Thyrotoxicosis</td>
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<tr>
<td>Premature menopause (&lt; 40 yrs)</td>
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<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Rheumatologic/autoimmune diseases</th>
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<tbody>
<tr>
<td>Celiac disease / IBS</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Gastric bypass</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>Systemic lupus</td>
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<thead>
<tr>
<th>Miscellaneous conditions and diseases</th>
<th>Medications</th>
</tr>
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<tbody>
<tr>
<td>AIDS/HIV</td>
<td>Aluminum (in antacids)</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>Anticonvulants</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
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<tr>
<td></td>
<td>Thiazolidinediones</td>
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<td></td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>(≥ 5mg/d prednisolone for ≥ 3 m)</td>
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<tr>
<td></td>
<td>Thyroid hormones (in excess)</td>
</tr>
</tbody>
</table>

## Risk factors for falls

<table>
<thead>
<tr>
<th>Environmental risk factors</th>
<th>Medical risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of assistive devices in bathrooms</td>
<td>Age</td>
</tr>
<tr>
<td>Loose throw rugs</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Low level lighting</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Obstacles in the walking path</td>
<td>Depression</td>
</tr>
<tr>
<td>Slippery conditions</td>
<td>Vitamin D insufficiency (serum 25(OH) D &lt; 30 ng/ml)</td>
</tr>
<tr>
<td></td>
<td>Malnutrition</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Neurological and musculoskeletal risk factors</th>
<th>Clinical risk factors included in the <strong>FRAX tool</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Kyphosis</td>
<td><strong>Rheumatoid arthritis</strong></td>
</tr>
<tr>
<td>Poor balance</td>
<td><strong>Secondary causes of osteoporosis:</strong></td>
</tr>
<tr>
<td>Impaired transfer and mobility</td>
<td>untreated long-standing hyperthyroidism,</td>
</tr>
<tr>
<td></td>
<td>hypogonadism or premature menopause</td>
</tr>
<tr>
<td></td>
<td>(&lt; 40 years), chronic malnutrition or</td>
</tr>
<tr>
<td></td>
<td>malabsorption, or chronic liver disease</td>
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</tbody>
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**Clinical risk factors included in the FRAX tool**

(Fracture Risk Assessment Tool)

<table>
<thead>
<tr>
<th>Current age</th>
<th>Rheumatoid arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td><strong>Secondary causes of osteoporosis:</strong></td>
</tr>
<tr>
<td>A prior osteoporotic fracture (including clinical and asymptomatic vertebral fractures)</td>
<td>untreated long-standing hyperthyroidism,</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²)</td>
<td>hypogonadism or premature menopause</td>
</tr>
<tr>
<td>Low body mass index (BMI, kg/m²)</td>
<td>(&lt; 40 years), chronic malnutrition or</td>
</tr>
<tr>
<td>Oral glucocorticoids ≥5 mg/d of prednisolone for &gt; 3 months</td>
<td>malabsorption, or chronic liver disease</td>
</tr>
</tbody>
</table>

**Parental history of hip fracture**

<table>
<thead>
<tr>
<th>Current smoking</th>
<th><strong>Alcohol intake</strong> (3 or more drinks/day)</th>
</tr>
</thead>
</table>

Laboratory testing for diagnosis secondary causes of osteoporosis

- **Blood or serum**: Complete blood count (CBC), Chemistry levels (calcium, phosphate, renal function, magnesium), Liver function tests, Thyroid-stimulating hormone (TSH) +/- free T4, 25(OH)D, Parathyroid hormone (PTH), Total testosterone and gonadotropin in younger man, Bone turnover makers

- **Consider in selected patients**: Serum protein electrophoresis (SPEP), serum immunofixation, serum-free light chains, Tissue transglutamine antibodies (IgA and IgG), Iron and ferritin levels, Homocysteine, Prolactin, Tryptase

- **Urine**: 24-h urinary calcium

- **Consider in selected patients**: Protein electrophoresis (UPEP), Urinary free cortisol level, Urinary histamine

Diagnosis assessment

- **Osteoporosis** is established by;
  - the measurement of BMD (DXA scan) or,
  - the occurrence of adulthood hip or vertebral fracture in the absence of major trauma

DXA scan: Dual energy x-ray absorptiometry

- Two photons are emitted from an x-ray tube
- Very precise measurements at clinically important sites with minimal radiation.
- Measures bone mineral density, approximation of bone mass
- Best predictor of fracture risk

Indication for “Bone mineral density” (BMD) testing

- In women age ≥ 65 and men age ≥ 70
- In postmenopausal women and men above age 50-69, based on risk factor profile
- In postmenopausal women and men age ≥ 50 who have had an adult age fracture
- At DXA facilities using accepted quality assurance measures
• Measurement: 
  *standard deviation of normal young subjects (T-score) and age-matched (Z-score)*

• T-score criteria of BMD at *femoral neck and lumbar spine for postmenopausal women and men age ≥ 50*

• *Z-score (ethnic/race adjusted) criteria for premenopausal women and men age < 50*
  – -2.0 or lower: below expected range of age
  – above -2.0: within the expected range of age

• *BMD of radius site (one-third) can be used when hip/lumbar cannot be measured*

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**WHO definition of osteoporosis by BMD**

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMD</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Within 1 SD of the mean level for a young-adult reference population</td>
<td>At -1.0 and above</td>
</tr>
<tr>
<td>Low bone mass (osteopenia)</td>
<td>Between 1.0 and 2.5 SD below that of the mean level for a young-adult reference population</td>
<td>Between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>2.5 SD or more below that of the mean level for a young-adult reference population</td>
<td>At or below -2.5</td>
</tr>
<tr>
<td>Severe or established osteoporosis</td>
<td>2.5 SD or more below that of the mean level for a young-adult reference population <em>with fractures</em></td>
<td>At or below -2.5 with one or more fractures</td>
</tr>
</tbody>
</table>

Vertebral imaging

• Vertebral fracture is consistent with a diagnosis of osteoporosis
• Proactive vertebral imaging is the only way to diagnose these fractures
• Presence of single vertebral fracture increases the risk of subsequent fractures 5-fold and the risk of hip and other fractures 2-3 fold
• Can be performed using a lateral thoracic/lumbar spine x-ray or lateral vertebral fracture assessment (VFA) from DXA

Vertebral Fracture- x-ray
Indication for “Vertebral imaging”

- All women age ≥ 70 and men age ≥ 80 if BMD T-score is ≤ -1.0 at spine, total hip, or femoral neck
- Women age 65 to 69 and men age 70-79 if BMD T-score ≤ -1.5 at spine, total hip, or femoral neck
- Postmenopausal women and men age 50 and older with specific risk factors
- If bone density testing is not available, vertebral imaging may be considered based on age alone


Indication for “Vertebral imaging”

- Specific risk factors
  - Low-trauma fractures during adulthood (age ≥50)
  - Historical height loss (difference between the current height and peak height at age 20) of 1.5 in or more (4 cm)
  - Prospective height loss (difference between the current height and a previously documented height measurement) of 0.8 in or more (2 cm)
  - Recent or ongoing long-term glucocorticoid treatment

Biochemical markers of bone turnover

- Can aid in risk assessment and serve as an additional monitoring tool when treatment is initiated
- **Resorption markers**
  - Serum C-telopeptide (CTX) and urinary N-telopeptide (NTX)
- **Formation markers**
  - Serum bone-specific alkaline phosphatase (BSAP), osteocalcin (OC), aminoterminal propeptide of type 1 procollagen (PINP)
- Best collected *in the morning while fasting*


**FRAX Score**

*calculate the 10-year probability of a hip fracture/and 10-year probability of major osteoporotic fracture*

- Threshold for treatment:
  - **3% Hip fracture, 20% Major osteoporotic fracture** in the next 10 years
FRAX Score

www.nof.org, www.shef.ac.uk/FRAX
FRAX Score

- FRAX is intended for postmenopausal women and men age ≥ 50, not for use in the young
- Can be calculated with either femoral neck BMD or total hip BMD, however, femoral BMD is preferred
- Therapeutic thresholds are for the clinician guidance only, not a rule

Management of osteoporosis

– Universal recommendations
– Pharmacological treatment

Universal recommendations

• Adequate amounts of total calcium intake
  – 1,000 mg/day for men 50-70 y
  – 1,200 mg/day for women ≥ 51 and men ≥ 71 y
  – including supplement if necessary

• Adequate vitamin D intake
  – 800-1,000 IU/d
  – including supplements if necessary for age ≥ 50 y

• Treatment of vitamin D deficiency
  – Treated 50,000 IU of vit D2 or vit D3 once a week or equivalent daily dose (7,000 IU) for 8-12 weeks to achieve a 25(OH)D ~ 30 ng/ml
  – Then maintenance of 1500-2000 IU/day or dose needed to maintain target blood level
Universal recommendations

• Regular weight-bearing and muscle-strengthening exercise
to improve agility, strength, posture/balance, maintain/improve
bone strength and reduce the risk of falls and fractures

• Assess risk factors for falls/ offer appropriate modifications;
  home stay assessment, balance training exercises,
correction of vit D insufficiency, avoidance of CNS depressant,
careful monitoring anti-HT, and visual correction

• Cessation of tobacco smoking

• Avoidance of excessive alcohol intake


Pharmacological treatment

• Initiate in those with
  – Hip or vertebral (clinical or asymptomatic) fractures
  – T-scores ≤ -2.5 at the femoral neck, total hip, or lumbar spine
    by DXA
  – Postmenopausal women and men age 50 and older with
    low bone mass (T score between -1.0 and -2.5, osteopenia)
    at femoral neck, total hip, or lumbar spine by DXA
    and 10-year hip fracture probability ≥ 3% or
    10-year major osteoporosis-related fracture probability ≥ 20%
    base on WHO FRAX

Current FDA-approved pharmacologic options

- **Bisphosphonates** (alendronate, ibandronate, risedronate, zoledronic acid)
- Calcitonin
- Estrogens and/or hormone therapy
- Tissue-selective estrogen complex (conjugated estrogens/bazedoxifene)
- Parathyroid hormone 1-34 (teriparatide)
- Receptor activator of nuclear kappa-B (RANK) ligand inhibitor (denosumab)


Bisphosphonates

- Generally 1st line
- Medications: alendronate, risendronate, zolendronic acid, ibandronate.
- Suppress bone resorption by preventing osteoclast attachment to bone matrix
- Decrease vertebral and non-vertebral in most
  - Reduction in fracture risk by approximately 50%
  - Non-vertebral fx prevention not proven for ibandronate
  - Zolendronic acid: 70% vertebral, 41% hip

Bisphosphonates

**Increase in bone mineral density (circles)**

**Decrease in urinary N-telopeptides (squares)**
**Bisphosphonates**

- Taken when "Empty stomach", first thing in the morning, with 8 oz of water
- After taking, should wait at least 30 min before eating/drinking and should remain upright (sitting/standing) during this interval
- Cannot be used with eGFR < 30-35%
- Side effects:
  - Esophagitis (not in IV forms)
  - Osteonecrosis of Jaw (ONJ), If duration > 5 y
  - Atypical femur fractures, If duration > 5 y


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**Denosumab (Prolia):**

- Humanized monoclonal antibody to RANK Ligand (Receptor activator of nuclear factor kappa-B ligand)
- Prevents formation of active osteoclasts
- Inhibits bone resorption

Lipton A, Smith MR, Ellis GK, Goessl C - Clin Med Insights Oncol (2012)
Pharmacological treatment

**Denosumab (Prolia):**

- Shorter biologic half-life than bisphosphonates
- **Reduces Fractures**
  - Vertebral by 68%
  - Hip by 40%
- Approved for women receiving aromatase inhibitors and men receiving Gn reducing treatment (CA prostate)
- **Contraindications:** *Current hypocalcemia, Pregnancy, hypersensitivity*

Denosumab (Prolia):

- **Potential Adverse Effects**
  - Atypical femur fractures
  - Osteonecrosis of Jaw
  - Possible increased risk of infections (cellulitis, endocarditis)
  - Suppression of bone turnover (delayed fracture healing)


Denosumab (Prolia):

- Change in bone density over time
Hormone Replacement Therapy:

• Estrogens +/- progesterones
• HRT was once considered to be the primary therapy of osteoporosis prevention/treatment
• Blocks cytokine signaling to the osteoclast
• Women’s Health Initiative trial: 34% reduction of hip fracture and vertebral fractures, but increased risk for breast cancer, cardiovascular disease, thrombosis...
• Currently, HRT is not used to treat or prevent osteoporosis alone (often used for other indications such as severe postmenopausal symptoms)

Teriparitide (Forteo)

• Stimulates bone remodeling by increasing bone formation
• Moderate to severe osteoporosis
• Reduction of fractures: 65% vertebral, 53% non-vertebral
• High doses in rats caused osteosarcoma but no cases of osteosarcoma seen in >200,000 pts. who received the drug
• Should not be given for more than 2 years
Teriparitide (Forteo)

- **Side effects:** mild hypercalcemia (10.5-11)
- Expensive and subcutaneous administration.
- Should **not be** given to patients with:
  - Hypercalcemia
  - Multiple myeloma, bone metastasis, skeletal tumor
  - Children/teenagers with growing bones

Duration of treatment

- **No pharmacologic therapy** should be considered indefinite in duration
- **No uniform recommendation** that applies to all patients and duration decisions need to be individualized
- Bisphosphonates may have *residual effects* after treatment discontinuation for several years
- Effects of all nonbisphosphonates wane upon discontinuation

Duration of treatment

- In modest risk of fracture, reasonable to **discontinue after 3-5 year** treatment period
- In high risk for fracture, **continue treatment** of bisphosphonate or alternative therapy

Monitoring patients

- **Perform BMD testing 1-2 years** after initiating medical therapy for osteoporosis and **every 2 years thereafter**
  - **More frequent BMD testing** may be warranted in certain clinical situations
  - The interval between repeat BMD screening may be **longer for pt without major risk factors** and have initial **T-score in normal/upper low range**

Monitoring patients

• Biochemical markers of bone turnover:
  – *Suppression of markers after 3-6 mths of treatment or*
  – *Increase of markers after 1-3 mths of anabolic hormone have been predictive of greater BMD response*

Summary

• *All postmenopausal women and men age ≥ 50 should be evaluated for osteoporosis risk, need for BMD testing and/or vertebral imaging*
• *Prevention:* adequate calcium/vit D/ weight bearing exercise
• *Screening BMD:* all women > 65 years, men > 70, women 50-64 with risk factors and patients on steroids/anti-estrogen treatment
• *Diagnosis:* screening by DEXA scan/diagnosis by WHO criteria
• *Treatment:* offered to patients; with a traumatic/low-impact fractures, with osteoporosis, with osteopenia and multiple risk factors.
Thank you for your attention.