Osteoporosis Diagnosis

Osteoporosis should be diagnosed based on:

- Presence of fragility fractures in the absence of other metabolic bone disorders
- T-score of $-2.5$ or lower in the lumbar spine (AP), femoral neck, total hip, and/or $33\%$ (1/3) radius even in the absence of a prevalent fracture
Osteoporosis may also be diagnosed in patients with osteopenia and increased fracture risk using FRAX country-specific thresholds.

**NBHA Position Statement: Clinical Diagnosis of Osteoporosis**

In postmenopausal women and men age 50 years and older, osteoporosis may be diagnosed by:

- T-score ≤ -2.5 at the LS, TH, or FN
- Low trauma hip fracture regardless of BMD
- Osteopenia with low trauma vertebral, proximal humerus, pelvis or some distal forearm fractures
- FRAX MOF risk ≥ 20% or HF risk ≥ 3%


**Implications of the New Clinical Definition**

- More patients will be labeled with the diagnosis
- Increased capture of high risk patients
- Increased coverage for DXA/labs and medications
- More accurate government cost appropriation for osteoporosis

**Case 1**

- 75 year old Caucasian female
- 140 lbs, 64 inches tall
- Maternal history of hip fracture
- No history of prior fractures
- No smoking, significant alcohol intake
- No RA, glucocorticoid use
- Lumbar spine T score -2.1, Femoral neck T score -2.3

- FRAX score: 14% major osteoporotic fracture and 4.5% hip fracture
- Thus she has “osteoporosis” based on new clinical definition
- DXA/labs can be covered as well as appropriate medications
Evaluation for Secondary Osteoporosis

- Complete blood cell count
- Serum chemistry, including calcium, phosphate, total protein, albumin,
- Liver enzymes, alkaline phosphatase,
- Serum creatinine, and electrolytes
- 24-h collection for calcium, sodium, and creatinine excretion
- Serum 25-hydroxyvitamin D

Causes of Secondary Osteoporosis

- Intact PTH
- TSH
- Tissue transglutaminase
- SPEP and free light chains
- Serum tryptase
- Urinary free cortisol
- Bone biopsy

Case 2

- 65 year old with no prior fractures
- Lumbar spine T score -2.5, Femoral neck T score -1.8
- Secondary workup revealed:
  - 25 OHD- 13 ng/ml
  - Intact PTH- 120 pg/ml (normal 10-65 pg/ml)
  - Serum calcium- 8.6 mg/dl, Phos- 2.9 mg/dl, 24 urine calcium- 95 mg/24 hours
  - Positive celiac antibodies
Case 2

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  - Intact PTH - 120 pg/ml (normal 10-65 pg/ml)
  - Serum calcium - 8.6 mg/dl, Phos - 2.9 mg/dl, 24 urine calcium - 95 mg/24 hours
- Positive celiac antibodies
- Would recommend correcting her vitamin D deficiency, secondary hyperparathyroidism and hypocalciuria
- Recommend GI biopsy/gluten free diet
- Ensure that the patient does not have osteomalacia by biochemical tests (high alkaline phosphatase)
- Antiresorptive therapy can later be started after repletion

INITIAL CHOICE OF AGENT

FDA Approved Agents and Effect on Fracture Risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vertebral Fracture</th>
<th>Nonvertebral Fracture</th>
<th>Hip Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitonin (Miacalcin®, Fortical®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Raloxifene (Evista)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ibandronate (Boniva®, generic)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Alendronate (Fosamax®, generic)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risedronate (Actonel, Atelvia, generic)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Zoledronic acid (Reclast, generic)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Teriparatide (Forteo®)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Current Medications for Osteoporosis

<table>
<thead>
<tr>
<th>Inhibit Bone Resorption</th>
<th>Stimulate Bone Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate (Fosamax, generic)</td>
<td>Teriparatide (Forteo)</td>
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<td></td>
</tr>
<tr>
<td>Calcitonin (Miacalcin, Fortical)</td>
<td></td>
</tr>
<tr>
<td>Estrogen (various)</td>
<td></td>
</tr>
<tr>
<td>Strontium (dual effect)</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations on initial choice of agent

- Approved agents with efficacy to reduce hip, non-vertebral, and spine fractures including alendronate, risedronate, zoledronic acid and denosumab, are appropriate as initial therapy for most patients at high risk of fracture
- Teriparatide, denosumab or zoledronic acid should be considered for patients unable to use oral therapy and as initial therapy for patients at especially higher fracture risk
- Raloxifene or ibandronate may be appropriate initial therapy, in some cases, for patients requiring drugs with spine-specific efficacy
**Risk Stratification**

- **Moderate fracture risk:**
  - Alendronate, risedronate, denosumab, or zoledronic acid
- **Higher fracture risk:**
  - Denosumab, teriparatide or zoledronic acid

**Higher fracture risk category:**

- Older age
- Prior fractures
- Very low T score
- High fall risk
- Glucocorticoids

**Case 3**
- 68 year old female with no prior fractures
- Lumbar spine T score -2.6, Femoral neck T score -2.4
- Maternal history of osteoporosis
- No other risk factors for fracture
- Secondary workup just showed vitamin D deficiency which has been corrected
- No GI issues

**Case 4**
- 85 year with multiple vertebral compression fractures, last one was 2 months prior
- Lumbar spine T score -3.3, Femoral neck T score -3.5
- Maternal history of hip fracture
- History or primary hyperparathyroidism s/p subtotal parathyroidectomy 6 years prior
- Secondary evaluation- vitamin D/calcium replete. The rest of the workup was fine.

**Treatment choices:**
- Oral bisphosphonates (alendronate or risedronate)
- If the patient is unable to tolerate oral BP’s, or as first line therapy: denosumab or zoledronic acid

**Patient has a very high fracture risk and is likely to suffer from another compression fracture**

**Treatment options:**
- Teriparatide, denosumab, zoledronic acid
RARE ADVERSE EVENTS

- Rare but Serious Adverse Events (SAEs), namely Atypical Femoral Fractures (AFF) and Osteonecrosis of the Jaw (ONJ), have raised concerns regarding the prolonged use of such drugs.

- The long term retention of BPs in bone, and the serious AEs, led to the concept of drug holiday, to maximize benefits and minimize harms.

OSTEONECROSIS OF THE JAW

- Osteonecrosis of the jaw (ONJ) definition:
  - The presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a healthcare professional.

- ONJ rarely associated with oral bisphosphonates:
  - Estimated between 1 in 10,000 and 1 in 100,000 patient-years.

- The ASBMR report recommends:
  "Patients should be informed that the risk of developing bisphosphonate-associated ONJ with routine oral therapy for osteoporosis or Paget’s disease seems to be low, ranging between 1/10,000 and 1/100,000 [per year]…" 

  *ASBMR = American Society for Bone and Mineral Research.

SUBTROCHANTERIC FRACTURES OF THE FEMUR

- Preliminary estimates of atypical femoral fracture incidence based on an HMO database (2.6 M people > 45).

- Progressive increase from 2 per 100,000 cases per year for 2 years of BP use to 78 per 100,000 cases per year for 8 years of BP use.

Bonus Features!

- Section on patient communication of rare adverse events
- Printable materials (www.empoweryourhealth.org) illustrating benefit/risk of treatment

DURATION OF THERAPY

Evidence used for recommendations

- FLEX trial
- HORIZON study extension
- Clinical experience

Clinical Vertebral Fractures in the FLEX Study

Recommendations on Optimum Duration of Therapy

- For oral bisphosphonates, consider a “bisphosphonate holiday” after 5 years of stability in lower-risk (or moderate risk) patients
- For oral bisphosphonates, consider a “bisphosphonate holiday” after 6 to 10 years of stability in higher-risk patients
- Treatment with teriparatide should be limited to 2 years

- For IV zoledronic acid, consider a drug holiday after 3 annual doses in lower-risk (moderate risk) patients and after 6 annual doses in higher-risk patients.
- Teriparatide or raloxifene may be used during the “bisphosphonate holiday” period for higher-risk patients.
Back to Case 3

- 68 year old female with no prior fractures
- Lumbar spine T score -2.6, Femoral neck T score -2.4
- Maternal history of osteoporosis
- No other risk factors for fracture
- Secondary workup just showed vitamin D deficiency which has been corrected
- No GI issues

Back to Case 4

- 85 year with multiple vertebral compression fractures, last one was 2 months prior
- Lumbar spine T score -3.3, Femoral neck T score -3.5
- Maternal history of hip fracture
- History or primary hyperparathyroidism s/p subtotal parathyroidectomy 3 years prior
- Secondary evaluation normal on calcium and ergocalciferol

ON COMBINATION THERAPY

- A drug "holiday" is not recommended with denosumab

- Treatment choices: oral bisphosphonates (alendronate or risendronate)
- If the patient is unable to tolerate oral BP’s, denosumab or zoledronic acid
- If on oral bisphosphonates ➔ drug holiday after 5 years
- If on zoledronic acid ➔ drug holiday after 3 years
- If on denosumab ➔ continuous therapy

- Patient has a very high fracture risk and is likely to suffer from another compression fracture
- Choice 1: Teriparatide
- Other options: Denosumab, zoledronic acid
- If on teriparatide ➔ stop at 2 years and switch to antiresorptive therapy
- If on denosumab ➔ continuous therapy
- If on zoledronic acid ➔ drug holiday after 6 years
AACE does not recommend concomitant use of antiresorptive agents for prevention or treatment of postmenopausal osteoporosis — (no fracture data)

If estrogen is being given for treatment of menopausal symptoms or raloxifene is being given to reduce the risk of breast cancer, an additional agent such as a bisphosphonate, denosumab, or teriparatide may be considered.

Secondary workup: 24 urine calcium 450 mg/24 hours.
Add antiresorptive therapy to her HRT
Start thiazide diuretic for idiopathic hypercalciuria

Case 5

47 year old female who had early menopause (age 35)
Was on HRT since menopause
Lumbar spine T score -3.6, Femoral neck T score -4.0
Family history of osteoporosis and kidney stones
No prior fractures or other causes of bone loss

Combined denosumab and teriparatide achieves improved BMD response versus either agent alone but no fracture data are available.
However this combination could be considered for patients failing denosumab

Effect of Combined Denosumab and Teriparatide

Leder, et al, JCEM 2014

ON SEQUENTIAL THERAPY
Treatment with teriparatide should always be followed by antiresorptive agents to prevent bone density decline and loss of fracture efficacy.

Several studies on teriparatide discontinuation showed BMD loss (PMO, premenopausal women, men) if not followed by antiresorptive therapy - Leder 2009, Cohen 2015.

Fracture
BMD decline
Rise in bone turnover markers may be a signal that the holiday should be over, but does not apply to those with low BTM’s prior to treatment.

When is the drug holiday over?

AACE/ACE 2016 POSTMENOPAUSAL OSTEOPOROSIS ALGORITHM
AACE/ACE Recommendations

- Risk stratification (no prior fractures and moderate fracture risk vs prior fractures and higher fracture risk) determines initial choice of therapy and duration of therapy.
- Moderate fracture risk: 5 years of oral BP, 3 years of ZA
- Higher fracture risk: 10 years of oral BP, 6 years of ZA

Duration of Treatment for Higher Fracture Risk Group

- Denosumab: continue therapy
- Teriparatide: continue therapy for up to 2 years, then sequential therapy
- ZA: continue therapy for up to 6 years, then drug holiday
- Consider using another agent during drug holiday

For patients who are losing bone on therapy or with recurrent fractures - moderate fracture risk group

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis
- If on oral BP, switch to injectable antiresorptive
- If on injectable antiresorptive, switch to teriparatide

For patients who are losing bone on therapy or with recurrent fractures - higher fracture risk group

- If on denosumab, consider adding teriparatide
- If on zoledronic acid, consider switching to teriparatide
How are patients monitored during drug holidays?
- Annual visits to assess clinical state and fractures
- DXA every 1-2 years
- Bone turnover markers
- Ensure vitamin D and calcium sufficiency
- Fall prevention advice

When is the holiday over?
- When a fracture occurs
- BMD loss beyond LSC
- BTM increase to pretreatment levels
- Clinically the patient’s fracture risk increases significantly (eg, treatment with high dose steroids, or significant increase in fall risk)

What happens after the drug holiday?
- Start another cycle of bisphosphonate therapy
- Patients who are at highest risk for fractures can be switched to anabolic therapy
- Patients previously treated with bisphosphonates can switch to denosumab

Conclusions
- Significant advances are happening in the diagnosis, prevention and treatment of osteoporosis
- The 2016 AACE/ACE Postmenopausal Guidelines have updated recommendations on the diagnosis, treatment and long term follow up of patients with osteoporosis
- Be sure to download your copy from aace.com

THANK YOU FOR YOUR ATTENTION