Bone and Diabetes

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Diabetes, Endocrinology & Metabolism

Faculty Disclosure

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Dr. Laura Graeff-Armas serves as a consultant for Midwest Dairy.

**AACE/ACE Guidelines**

**AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY**

**CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS — 2016**

**EXECUTIVE SUMMARY**

**Michael**

**Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society**

**Clinical Practice Guideline**

Richard Eastell,1 Clifford J. Roson,2 Dennis M. Black,3 Angela M. Cheung,4 M. Hasain Murod,5 and Dolores Shoback6,7

**Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline**


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**Osteoporosis is serious, even deadly.**

**EACH YEAR IN THE U.S., APPROXIMATELY 300,000 HIP FRACTURES OCCUR**

Approximately 75,000 Americans who experience a hip fracture die in the year following the fracture.

Another 75,000 Americans move from the hospital to a nursing home and never return “home.”

The remaining 150,000 Americans never regain their previous function. Six months after a hip fracture, only 15 percent of patients can walk across a room unaided.
Assess Fracture Risk

• ALL women >50 years
• History and Physical
• FRAX®
• When to do DXA
• Women $\geq$ age 65 or
• If younger than a fracture risk $\geq$ 65 year old

• Men $\geq$ age 70
• or 50-69 with risk factors

• When to do DXA
• Women $\geq$ age 65 or Men $\geq$ age 70

• Fragility fracture
• Steroids
• Osteopenia on X-ray
• Clinical Risk factors: low body weight (<127 lbs), smoking, family history, early menopause, secondary osteoporosis
Bone Mass Measurement

Spine or L1-L4  
Total Hip, total femur or femoral neck

Bone Mass Measurement

Spine T-Score, -0.7  
Spine Z-Score, +0.6
Osteoporosis Diagnosis

• T-score ≤ -2.5

• Or fragility fracture (trauma < falling from standing height)

• Or FRAX score > 20% for major osteoporotic fracture or > 3% for hip fracture.

Evaluation of Osteoporosis

| Diabetes mellitus | Alcoholism | Anorexia nervosa | Chronic liver disease | Malabsorption syndromes/ malnutrition (including celiac disease, cystic fibrosis, Crohn’s disease, and gastric resection or bypass) | Total parenteral nutrition | Vitamin D deficiency | Anti-epileptic drugs* | Anorexia inhibitors | Chemotherapy/immunosuppressants | Dips-Pravasen | Euthyroid hyperthyroidism | Gastrointestinal hormone agents | Hip pain | Pantothenic acid inhibitors | Selective serotonin reuptake inhibitors | Thiazolidinediones | Thiomersal | Tissues

Gut absorption, inflammatory, estrogen
Reasonable Workup

• CBC
• CMP
• 25(OH)D
• Phosphorus

• PTH
• 24 hour urine calcium, creatinine
• Suspicious - TSH, celiac, SPEP, Testosterone (men)

Vertebral Fracture Assessment

• Lateral spine imaging
• T-score <= -1.0
• And
  – Women > 70 or men > 80
  – Height loss > 1.5 inches
  – Self reported vertebral fracture
  – Prednisone equivalent > 5 mg for > 3 months
Bone Markers & Remodeling

***BSAP – Bone Specific Alkaline Phosphatase

Common sense

• Calcium and vitamin D
• Exercise
• Minimize falls
• Stop smoking
• Avoid excessive Etoh
Calcium

• 2011 Institute of Medicine report indicated that daily intake of **1,200 mg** of calcium (vitamin D) for women ages 51 to 70 had a clear net benefit in fracture prevention (15-30%).

• Recommend dietary Ca\(^{2+}\), keep supplements <1000 mg/day

• All osteoporosis meds were tested with Calcium as co-therapy

Institute of Medicine 2011 DRI's for calcium and vitamin D.
The National Academies Press.

Vitamin D

• 25(OH)D Goal 30-50 ng/ml (**40**)

• Dosing Rule of thumb:
  • 1000 IU vitamin D\(_3\) increases 25(OH)D by 10

• Can use Bolus dosing
  – 50,000 weekly for 8-12 weeks
  – Or 5,000 daily for 8-12 weeks

If they are really low <10-15 without obvious cause, check other reasons celiac
**PROTEIN INTAKE & BONE LOSS**

RDA Adequate Protein = 0.8 g/kg

- Framingham osteoporosis cohort (75 yr)
- bone loss as a function of protein intake (by quartiles)
- diet protein mostly of animal origin

![Graph showing bone mineral density (BMD) changes in femoral neck by protein intake quartiles.]

*Hannam et al., JBMR 2000

**Diabetes and Bone**
Fractures

- T1DM at higher risk (double?) of their age group
- T2DM at increased risk (15-30% higher)
- Associations with longer DM duration, poor glycemic control, retinopathy and neuropathy
- Prolonged fracture healing
Bone Mass (BMD by DEXA)

- T1DM usually lower
- T2DM actually have *higher* BMD

So if fracture isn’t related to bone mass in diabetics?...
It’s a Bone Quality Issue

Other Measures

- Cortical Porosity
Trabecular Bone Score (TBS)

Bone Remodeling
Bone Remodeling

• Diabetes may cause low bone turnover – with poor bone resorption and formation

Why???

• Hyperglycemia-
  – Excess glucose forms advanced glycation end products which makes the bone more brittle

• Microvascular Disease
  – Shifts bone progenitor cells away from OB to form fat cells
What to do about it?

• Good glycemic control
• Avoid TZDs and SGLT2 meds
• Lifestyle – increase muscle strength and balance and vitamin D and calcium
• Treat according to general osteoporosis guidelines.

Case 1
• HPI – 45 yr old female with T1DM since age 13. Poorly controlled most of life. HgA1c 8%

• Currently seen for humerus fx >2 yrs ago, nonunion
• Fractured multiple times – femur and tib/fib
• Perimenopausal – on estrogen
• DEXA unable to obtain

• Labs
• BSAP 13.7 bone formation marker
  – (premenopausal range 4.5-16.9, Postmenopausal range 7.0-22.4)

• CTX 458 bone resorption marker
  – (range 40-465)
• Because of her history of nonunion and low remodeling markers with non healing fracture and T1DM may have low remodeling

• -started on teriparatide – anabolic agent

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**Case 2**

• 69 yr old female with T2DM for 15 years,
• On insulin with HgA1c 7%-11%
• HTN, CAD, CVA
• With renal disease GFR ~30
• Fell and broke her pelvis. Hx of leg, wrist and ankle fractures
DEXA

![DEXA Images]

### Table

<table>
<thead>
<tr>
<th>Region</th>
<th>BMD (g/cm²)</th>
<th>Z-score</th>
<th>Age-Matched Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>1.21</td>
<td>3.8</td>
<td>0.5</td>
</tr>
<tr>
<td>L2</td>
<td>1.22</td>
<td>3.1</td>
<td>0.5</td>
</tr>
<tr>
<td>L3</td>
<td>1.24</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>L4</td>
<td>1.27</td>
<td>0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>L5-L4</td>
<td>1.25</td>
<td>0.2</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### AP Spine L1-L4 (BMD)

- BMD (g/cm²)
- Z-score
- Age-Matched Z-score

### AP Spine L1-L4 (BMD) %Change vs Baseline

- Baseline: X
- Change: Y
Labs

- 25(OH)D – 16 (goal ~40ng/ml)
- Calcium 9.1
- Albumin 4
- PTH 94 (range 12-88)

- BSAP 23.7 (Postmenopausal range 7.0-22.4) – 6 weeks after fracture

FRAX
Treatment

- Calcium and Vitamin D
- Oral bisphosphonate – 1st line – compliance and absorption
- Reclast contraindicated with her level of kidney disease
- Prolia – approved with CKD
• Who?
• Fragility Fracture (esp within 2 years)
• T-score < -2.5
• FRAX score > 20% for major osteoporotic fracture or > 3% for hip fracture.

• Steroids (prednisone equivalent > 7.5 mg/day)*

*Endo Society and AC of Rheumatology
**Current Treatments for Osteoporosis**

- **Bisphosphonates**
  - *Alendronate*
  - *Risedronate*
  - Ibandronate
  - Zolendronic Acid

- **SERMs**
  - Raloxifene
  - Bazedoxifene/estrogen

- **HRT/ERT** – various combos of estrogen, oral and transdermal

- **Denosumab**

**Anabolic Agents:**

- Teriparatide
- Abaloparatide
- Romosozumab

**ENDO Society 2019**

- All Postmenopausal Women
  1. Lifestyle and Nutritional Optimization for Bone Health Especially Calcium and Vitamin D
  2. Determine the 10-year Fracture Risk According to Country-Specific Guidelines

**Low-Moderate Risk**

- Assess fracture risk in 2-4 yrs
  - 2-3: Consider a drug holiday
  - 3: Reassess fracture risk every 2-4 yrs
  - 4: Bone loss or patient becomes high risk, consider restarting therapy

**High-Risk**

- Reassess fracture risk in 2 yrs
  - High-very High Risk
  - For 2 yrs
  - Consider giving bisphosphonates and then stopping for a drug holiday
  - For 2 yrs
  - Reassess fracture risk every 1-3 yrs
  - If bone loss, fracture occurs, or patient becomes high risk, consider restarting therapy

**Low-Moderate Risk**

- Assess fracture risk in 5-10 yrs
  - Low, Very Low Risk
  - For 5 yrs
  - Reassess fracture risk every 5 yrs
  - For 5 yrs
  - Reassess fracture risk every 5 yrs

**High Risk**

- Consider going to an alternative agent
  - High, Very High Risk
  - For 2 yrs
  - For 2 yrs
  - For 2 yrs
  - For 2 yrs

**Injectables – higher risk**

- GI problems
  - Trouble remembering

**Oral – those at lower fracture risk**

- Trouble remembering
Bisphosphonates

• Oldest class of bone antiresorptives
• Generic alendronate and ibandronate available
  – Oral (Alendronate, Risedronate, Ibandronate)
    • MUST take fasting and wait 30-60 minutes
    • Contraindicated – esophageal disease, GI malabsorption, can’t sit upright
  – IV (Ibandronate, Zolendronate)
    • Acute phase reaction
    – Renal disease GFR <30-35 contraindicated
• Inhibit osteoclasts, preserve osteoblasts

Ibandronate not FDA approved in men

SERMS

• Selective estrogen receptor modulators
• Raloxifene
  • Prevents fracture (spine), breast cancer
  • Risk of blood clots, hot flashes

• Bazedoxifene/conjugated equine estrogen
  • Maintains BMD, prevents hot flashes
  • Approved for osteoporosis prevention

not FDA approved in men
HRT/ERT

• While *not approved* for osteoporosis Rx by FDA, Endo Society rec in select patients
• It does prevent fracture & maintains BMD
• younger (50-59) women
• It prevents hotflashes

*not FDA approved in men*
• Denosumab
• Can cause hypocalcemia (hypophosphatemia) if vitamin D and calcium deficiency not fixed, CKD
• No drug holiday
• Have to be given on time
• No residual protection, may even increase rates fracture after stopping

Teriparatide

• Recombinant PTH 1-34
• Anabolic – stimulates bone formation and bone turnover
• High fracture risk or “failed’ other Rx
• 2 years
• Side effects – $$$, hypercalcemia, daily injections
• Contraindicated – HPT, Paget’s, radiation to skeleton
Abaloparatide

- Synthetic analog of PTHrP
- Daily SQ injections

Active Trial Results

- 18 months
  - daily abaloparatide 80mcg SC,
  - placebo SC,
  - open-label teriparatide (TPTD) 20mcg SC.

- 70% reduction in major osteoporotic fractures
Sclerostin

Sclerostosis and van Buchems disease - deficiency of sclerostin

- Sclerostin - inhibitor of bone formation
- Romosozumab – antibody to sclerostin
  – Monthly SQ injection
FRAME trial results

- February 2016- preliminary results, Phase 3 trial
- 12 months of monthly SQ romosozumab followed by 12 months of Prolia
- significantly reduced the risk of vertebral fractures (73%)
- But didn’t significantly reduce non-vertebral fracture

Calcitonin

- Nasal spray
- ? Vertebral fractures
- No hip or non-vertebral fracture efficacy
- ? May help with acute pain after vertebral fracture
- Recommended as very last line in someone who can't do anything else

not FDA approved in men
Risk categories

“Low risk”
- No hip or spine fx
- T-score > -1.0
- FRAX <3% hip, <20% other

“Moderate risk”
- No hip or spine fx
- T-score > - 2.5 or
- FRAX <3% hip, <20% other

“High risk”
- Prior hip or spine fx or
- T-score < -2.5 or
- FRAX ≥3% hip, ≥20% other

“Very high risk”
- Multiple spine fx
- T-score < -2.5
- FRAX >3% hip, >20% other
Drug Holidays

- Only bisphosphonates
- “Low risk” (no fracture, T-score >= -2.5)
  - 5 years oral, 3 years IV
- “High risk” (prior fracture, T-score <= -2.5)
  - 10 years oral, 6 years IV, no holiday, switch to another agent.

- Duration of Holiday – max 5 years, fx start 2 years after stopping Rx, restart if losing bone, fx, risk changes

There are about 2.3 million adults treated in ERs each year for injuries from MVAs and about 2 million osteoporotic fractures each year. The risk of seat belt injuries and serious side effects from osteoporosis treatment is very small in proportion to the benefits. Data from multiple sources.
Men & testosterone

- T <200 ng/dl associated with BMD decrease
- Consider replacing
- High risk for fracture – treat with osteo drug

While BMD can improve with T, no fracture data

Atypical Fractures

Radiographic appearance and characteristics of a typical vs. atypical subtrochanteric fracture (courtesy of Dr. Melvin Rosenwasser, Columbia University, New York, NY).
Atypical Fracture: 2013

• The consensus is these fractures are very similar to stress fractures
• There is an association with Bisphosphonates
• Although atypical fractures w/o Bisphosphonates is not uncommon
• Overall absolute risk for patients is low
  – 3-50 cases per 100,000 person years

Osteonecrosis of the Jaw

ASBMR Task Force JBMR January 2014
Osteonecrosis of the Jaw

- Known risk factors for ONJ include:
  - Diagnosis of cancer
  - Concomitant therapies (eg, chemotherapy, radiotherapy, and corticosteroids)
  - Poor oral hygiene
  - Comorbid disorders (eg, pre-existing dental disease, anemia, coagulopathy, and infection)
- The mechanism by which ONJ occurs is currently uncertain.¹

Bisphosphonates & Osteoporosis

- ONJ occurs in the population without exposure to bisphosphonate.
- The risk of ONJ in a population is estimated to be 1/1,000-260,000 person years in patients treated with an oral bisphosphonate.

### Osteonecrosis of the Jaw: Comparative Risks

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk per 100,000 People per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Fragility Fracture (1)</td>
<td>2668</td>
</tr>
<tr>
<td>Hip Fracture (1)</td>
<td>387</td>
</tr>
<tr>
<td>Anaphylaxis from PCN Shot</td>
<td>32</td>
</tr>
<tr>
<td>Death by MVA</td>
<td>11</td>
</tr>
<tr>
<td>Death by Murder</td>
<td>6</td>
</tr>
<tr>
<td>ONJ- Osteoporosis Patient</td>
<td>0.7</td>
</tr>
<tr>
<td>Death by Lighting Strike in NM</td>
<td>0.6</td>
</tr>
</tbody>
</table>

(1) Women age 65-69 (from Swedish National Bureau of Statistics and database of Olmsted County, MN, USA.)

Kanis JA et al. Osteoporos Int. 2001
JADA. 2006;137:1144-1150.

### Osteoporosis is treatable, if not preventable.

**84% NOT TESTED OR TREATED**

The disease is responsible for an estimated two million broken bones per year, yet nearly 84 percent of older Americans who suffer bone breaks are not tested or treated for osteoporosis.

**50% OF REPEAT FRACTURES COULD BE AVOIDED**

with cost-effective and well-tolerated treatments
Structure of a Hospital-Based FLS

* Older patients, where appropriate, are identified and referred for falls assessment
Adapted from BOA-BGS 2007 Blue Book. http://www.nhfd.co.uk/

New Fracture Presentation

Emergency Department & X-Ray

Orthopaedic Trauma

Orthopaedics Inpatient ward

1. FLS identifies fracture patients
2. FLS assessment

Emergency Department

Outpatient Fracture clinic

Osteoporosis treatment

Falls risk assessment*

Exercise programme

Education programme

Nutrition

Comprehensive communication of management plan to GP supported by fully integrated FLS database system

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