Session 8:  
ACP Featured Speaker:  
Primary Care Update on Osteoporosis

Learning Objectives

1. Review information about prevention of osteoporosis, including recommendations about calcium and vitamin D intake.
2. Review current treatment options and duration of therapy for osteoporosis.
Dona Gray attended the University of Notre Dame. Following graduation from the Indiana University of Medicine, she completed her internal medicine residency at St. Vincent Hospital in Indianapolis, Indiana. Her diabetes, endocrinology and metabolism fellowship was completed at Indiana University. She is currently in the private practice of endocrinology in Lafayette, Indiana.

Faculty Financial Disclosure Statement
The presenting faculty reports the following:
Dr Gray receives a speaking fee from sanofi-aventis.
Primary Care Update on Osteoporosis

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Lafayette, Indiana
October 5, 2012

Objectives

- Review information about prevention of osteoporosis.
- Review recommendations about calcium and vitamin D intake.
- Review current treatment options and duration of therapy for osteoporosis.

Scope

- An estimated 10 million individuals have osteoporosis and another 34 million have low bone mass.
- 2 million fractures each year
  - 600,000 of those are in men

Osteoporosis

- Skeletal disorder of architectural disruption, decreased bone strength, imbalanced bone remodeling, and increased chance of fracture
- Fracture = “Bone attack”
  - 50% individuals have low bone mass


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Bone Density Report

- Density is reported in grams/cm²
- T-score
- Z-score:
  - (Look for secondary causes if −2)
- For every 1 SD below the mean:
  - 2.3 relative risk of vertebral fracture
  - 2.6 relative risk of hip fracture

Labs to Consider

- Calcium, phosphorus, creatinine
- Alkaline phosphatase
- Liver function
- 25-hydroxy vitamin D
- Testosterone (in men)
- CBC
- Urine calcium excretion
- PTH
- Cortisol
- Thyroid levels
- Transglutaminase antibody


Audience Response Question

- A healthy post-menopausal female wants your recommendation for calcium and vitamin D supplementation.
- According to the USPSTF recommendations, you tell her to take:
  1. 1500 mg calcium per day
  2. 1200 mg calcium per day
  3. 1000 mg calcium per day
  4. No extra calcium supplementation

USPSTF = US Preventive Services Task Force

http://www.uspreventiveservicestaskforce.org/uspstf12/vitamind/vitdart.htm

USPSTF Draft Recommendation:
No Vitamin D, Calcium Supplementation for Healthy Post-menopausal Women

- Healthy post-menopausal women should not take daily low-dose vitamin D and calcium supplements to prevent fracture (grade D recommendation).
- 400 IU of vitamin D³ and 1000 mg of calcium carbonate taken daily do not reduce osteoporotic fractures and may slightly increase the risk for kidney stones.
- USPSTF does not recommend vitamin D and calcium supplementation to prevent fractures in men or pre-menopausal women.

Points of Confusion

- IOM recommends minimum of 20 ng/mL.
- However, levels over 30 ng/mL are recommended by other societies for optimal bone health.

IOM = Institute of Medicine

http://www.uspreventiveservicestaskforce.org/uspstf12/vitamind/vitdart.htm
Society Guidelines for Vitamin D

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommended Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ministry of Health of New Zealand</td>
<td>200–600 IU</td>
</tr>
<tr>
<td>Standing Committee of European Doctors</td>
<td>600–800 IU</td>
</tr>
<tr>
<td>Institute of Medicine</td>
<td>600–800 IU</td>
</tr>
<tr>
<td>International Osteoporosis Foundation</td>
<td>800–1000 IU</td>
</tr>
<tr>
<td>Endocrine Society</td>
<td>1500–2000 IU</td>
</tr>
<tr>
<td>American Association of Clinical Endocrinologists</td>
<td>1000–2000 IU/day to maintain level over 30 ng/mL</td>
</tr>
</tbody>
</table>

National Osteoporosis Foundation (NOF) Recommendations

- At least 1200 mg calcium per day
- 800–1000 units of vitamin D per day for patients aged over 50 years

Cumulative Percentage of All 389 Subjects with a First Nonvertebral Fracture, According to Study Group

Prevalence of vitamin D inadequacy in all subjects

Effect of Vitamin D2 or D3 on Serum 25(OH)D

High Doses of Vitamin D Linked to Modestly Reduced Fracture Risk

- Analysis of 11 studies of over 31,000 people aged 65 and older who were randomized to oral vitamin D supplements or placebo.
- In patients in the highest actual-intake quartile (792 to 2000 IU daily), there was a 30% reduction in hip fracture incidence, relative to controls.
- The highest intake conferred a 14% risk reduction for any nonvertebral fracture. There were no significant reductions in fracture risk at lower intakes.
Calcium supplements, but not dietary calcium intake, are associated with elevated risk for myocardial infarction.

- Effect of calcium intake on 24,000 participants in a German study of cancer and nutrition.
- During an average follow-up of 11 years, there were 354 myocardial infarctions (MIs), 260 strokes, and 267 cardiovascular (CV) deaths.
- There was no evidence of increased risk for MI, stroke, or CV mortality with increasing dietary calcium intake.
- However, use of calcium supplements was associated with significantly elevated risk for MI (hazard ratio, 1.86), but not stroke (HR, 1.05), or CV death (HR, 1.02), although the number of events in supplement users was small.


Vitamin D Supplementation

- 1000 units/day = 6 ng/mL increase in 25 vitamin D levels, on average.
- Target is 30–60 ng/mL.


Calcium and Vitamin D

- Ensure at least 1200 mg per day of calcium intake, preferably from diet.
- At least an extra 1000 units of vitamin D per day for most patients.


NOF Recommendations

- Three or four 30 minutes weight-bearing activities each week.
- Smoking cessation.
- Fewer than 3 alcoholic drinks/day in men, 2 in women.


Reduction of Vertebral Fracture Risk in Postmenopausal Women with Osteoporosis Treated with Raloxifene: Results from a 3-Year Randomized Clinical Trial


MORE = Multiple Outcomes of Raloxifene Evaluation
Treatment of Osteoporosis

According to NOF guidelines, who would you NOT treat with pharmacologic therapy:
1. 80-yo female with T-score of –2.8 in femur
2. 52-yo female with T-score of –1.7 in hip and 10-yr osteoporosis fx risk of 22%
3. 63-yo female with T-score of 2.3 in hip and 10-yr risk of hip fx of 2.5%
4. 68-yo female with history of compression fracture and T-score of –2.2 in spine

FRAX

Audience Response Question
FRAX calculations use the following data points EXCEPT:
1. Age
2. Alcohol use
3. Lumbar spine bone-mineral density
4. Smoking
5. Rheumatoid arthritis

FRAX Helps Determine Who to Treat
- FRAX scores
  - Femoral neck density
  - Prior fracture
  - Parental hip fracture history
  - Age
  - Gender
  - Body mass index
  - Ethnicity
  - Smoking
  - Alcohol
  - Steroid use
  - Rheumatoid arthritis
  - Secondary osteoporosis

Treatments
- Diet with Adequate Calcium and Vitamin D
- Exercise
  - 30 minutes, 3 days a week
- Smoking Cessation
  - 1 pack/day as an adult decreases bone density 5% to 10%
- Pharmacologic Treatments

Exercise Guidelines
- Patients with spinal fractures should avoid horseback riding, golf, tennis, and bowling.
- Patients with osteoporosis of the spine should avoid exercise machines that cause spinal flexion, trunk rotation, and forward bending.
NOF Guidelines for Pharmacologic Intervention in Post-menopausal Women and Men ≥ 50 Years of Age

- History of hip or vertebral fracture
- Other prior fractures and T-score between −1.0 and −2.5 at the femoral neck, total hip, or spine by DEXA
- T-score ≤ −2.5 (DEXA) at the femoral neck, total hip, or spine, after appropriate evaluation to exclude secondary causes


Classes of Pharmacologic Treatment

- Calcitonin
- Estrogen
- SERMs
- Anabolic therapy
- Oral bisphosphonate
- IV bisphosphonate
- RANKL inhibitor

Calcitonin

- Made by C-cells in the thyroid
- Decreases osteoclast activity

Raloxifene

- Selective estrogen receptor modulator
- Estrogen-like effects on bone
- Lacks estrogen effects on uterus and breast
- Lowers cholesterol and LDL


Raloxifene’s Effect on Spine and Femoral Neck
**Oral Bisphosphonates**

**Audience Response Question**

A post-menopausal female who has taken alendronate for 5 years asks for recommendations. What do you tell her?

1. Continuing treatment will not reduce vertebral fracture risk
2. Treatment should be continued indefinitely
3. If her pre-treatment T-score was −1.9 and she did not have a fracture, it would be acceptable to take a drug holiday
4. Regardless of her baseline T-score, since she has had 5 years of therapy, it would be okay to stop the medication

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**IV Bisphosphonates**

**Audience Response Question**

A patient with severe GERD has been receiving an IV bisphosphonate infusion for the last 3 years. Her GFR is 34 mL/min. She comes to see you to discuss this year’s therapy. You tell her:

1. We are ready to proceed.
2. Continuing therapy will reduce risk of future symptomatic vertebral fracture.
3. Zolendronic has been studied for up to 8 years of therapy.
4. With no prior fracture history, she can take a drug holiday now.

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**Bisphosphonate Therapy:**

**For Whom and How Long?**

Current evidence supports the following:

- Patients with low BMD at FN (< −2.5) after 3 to 5 years treatment are at highest risk for vertebral fracture and appear to benefit most from continuing treatment.
- Patients with existing vertebral fracture who have somewhat higher (not higher than −2.0) BMD may benefit from continuing therapy

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**Bisphosphonate Therapy (con’t.)**

- Patients with FN T-score above −2.0 have low risk of vertebral fracture and unlikely to benefit from continued treatment.
- When to reinstitute treatment is unclear and awaits further study.

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**Osteonecrosis of the Jaw**

- ASBMR: Area of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health care provider ...
- ... in a patient who was receiving or had been exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region.

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**Osteonecrosis of the Jaw**

- Estimated incidence of 1% to 10% in patients receiving monthly IV bisphosphonates therapy for metastatic bone disease
- Estimated incidence 1:5000 to 1:100,000 patient years of bisphosphonates for osteoporosis
- Most cases occur after invasive dental procedures
- Recently reported in cancer patients treated with denosumab

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GERD = gastroesophageal reflux disease
GFR = glomerular filtration rate

**References:**

Osteonecrosis of the Jaw

- Known risk factors:
  - Diagnosis of cancer
  - Chemotherapy, radiotherapy, corticosteroids
  - Poor oral hygiene
  - Smoking
  - Co-morbidities: pre-existing dental disease, anemia, infection, coagulopathies


Bisphosphonate Use Linked to Atypical Fractures

This anterior-posterior radiograph of the left femur demonstrates a substantially transverse femoral fracture and associated diffuse periosteal new bone formation (black arrow) and focal cortical thickening (white arrow), consistent with atypical femoral shaft fracture.

Source Courtesy American Society for Bone and Mineral Research

Atypical Femur Fractures: Major Features

- Located anywhere along the femur from just distal to lesser trochanter to just proximal to supracondylar flare
- Associated with no or minimal trauma, as in a fall from standing height or less
- Non-comminuted, transverse or short oblique configuration

Atypical Femoral Shaft Fractures

- Proposed Mechanism
  - Excessive bone suppression causing accumulation of micro-fractures and increased skeletal fragility

Audience Response Question

75-yo female with a history of esophagitis has a DEXA with a T-score of –2.8. Routine lab work shows normal thyroid function, calcium level, a creatinine 0.91, and a GFR of 32 mL/min. Which treatment do you recommend?

1. No treatment
2. Calcium and vitamin D only
3. Oral bisphosphonate
4. IV bisphosphonate
5. RANKL inhibitor (denosumab)

Denosumab

- Human monoclonal antibody that targets the receptor activator of nuclear factor-kappa B ligand (RANKL)
- RANKL is a cytokine member of the tumor necrosis family (TNF) that is the final principal mediator of osteoclastic bone resorption
- Denosumab prevents RANKL from binding to its receptor on the surface of osteoclasts and their precursors
**Denosumab**
- Does not become incorporated into bone, and bone resorption markers return to baseline 6 months after the last injection
- Unaffected by renal impairment

**Denosumab: Adverse Events**
- Serious skin infections (cellulitis, eczema), as well as infections of the abdomen, urinary tract, and ear were more frequent in denosumab group.
- Eczema (118 vs 65): cellulitis (12 vs 1)
- Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk
- ONJ has been reported in cancer trials.

**Osteoporosis In Men**
- Alendronate
- Risdedronate
- Zoledronic acid
- Teriparatide
- Denosumab for men at high risk of fracture who are receiving androgen-deprivation treatment (ADT) for prostate cancer

**Testosterone and BMD**
- Increases BMD in men with levels below 200 ng/dL
- No fracture data
The testosterone treatment effect on percent change in bone mineral density during 36 months of testosterone treatment in men over 65 years of age as a function of the pre-treatment serum testosterone concentration.


76-yo female with history of osteoporosis treated with oral bisphosphonate for two years recently had a vertebral fracture. Which of the following has the most likelihood of improving bone density?

1. Changing to a different oral bisphosphonate
2. Changing to IV bisphosphonate
3. Teriparatide
4. Calcitonin treatment to help pain

Teriparatide
- Stimulates bone formation
- Activates bone remodeling
- Administered subcutaneously as daily injections

Teriparatide Candidates
- Men or post-menopausal women with severe osteoporosis (T-score of –3.5 or below, even in the absence of fractures; T-score of –2.5 or below, plus a fragility fracture)
- Patients with osteoporosis who are unable to tolerate bisphosphonates or who have relative contraindications to bisphosphonates (achalasia, scleroderma esophagus, esophageal strictures)
- Patients who fail other osteoporosis therapies (fracture with loss of BMD in spite of compliance with therapy)


Unsuitable Teriparatide Candidates
- Patients with primary or secondary hyperparathyroidism
- Patients who are at increased baseline risk for osteosarcoma
  - Paget's disease of bone
  - History of prior radiation therapy
  - Unexplained elevation of alkaline phosphatase

Having Second Thoughts ...
- In patients with pre-existing malignancies, renal stones, gout, or renal insufficiency
- Unless other drugs have failed AND the benefits of teriparatide outweigh potential risks
Summary of Drug Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>LS BMD</th>
<th>Hip BMD</th>
<th>Fx Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>6%</td>
<td>4%</td>
<td>50% spine 30% hip 30% non-vert</td>
</tr>
<tr>
<td>Risedronate</td>
<td>5%</td>
<td>3%</td>
<td>40% spine 30% hip 30% non-vert</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>5%</td>
<td>4%</td>
<td>50% spine</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>7%</td>
<td>6%</td>
<td>70% spine 40% hip 25% non-vert</td>
</tr>
</tbody>
</table>


Duration of Therapy

- Calcitonin: No limit – data up to 5 years
- Raloxifene: No limit – data up to 8 years
- Oral bisphosphonates: Reassess after 5 years
- IV bisphosphonates: Reassess after 3 years
- Teriparatide: Lifetime limit of 24 months
- Denosumab: Data up to 6 years

Conclusions

- Calcium and vitamin D intake should be monitored and discussed
- Be aware of the risks and side effects of medications
- Consider drug holidays for those at low risk of future fractures

Thank you!

Questions?
<table>
<thead>
<tr>
<th>Bone Turnover Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formation</strong></td>
</tr>
<tr>
<td>• Bone-specific alkaline phosphatase (BSAP)</td>
</tr>
<tr>
<td>• Osteocalcin</td>
</tr>
<tr>
<td>• Propeptide of type I collagen (P1NP)</td>
</tr>
<tr>
<td><strong>Resorption</strong></td>
</tr>
<tr>
<td>- N-telopeptide of type I collagen (NTX): urine test</td>
</tr>
<tr>
<td>- C-telopeptide of type I collagen (CTX): blood test</td>
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