“SpongeBone” Menopants*

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Kettering Health Network

*Postmenopausal Osteoporosis
Objectives

- Epidemiology
- Clinical significance
- Pathophysiology
- Screening and Diagnosis
- Treatment modalities
- Side effects
Background

- ~1.5 million osteoporotic fractures/year
- 10 million with osteoporosis
- 34 million with osteopenia
- Most → postmenopausal women
- Bone mass and bone quality
- Qualitative changes in microarchitecture
  - Bone remodeling in dynamic equilibrium
  - Peak BMD at age 30
- 50 year old WF
  - 15-20% → hip fx
  - 50% → any osteoporotic fx
Hip fracture

- Older women who have hip fracture have a 2-3 fold increase in death in one year
- 1 month after surgery 10.5%
- 6 months 21.5%
- 1 year 27.3%
16% → vertebral fx
18% → hip fx
16% → wrist fx

40% → one of these fxs
Complications of Osteoporosis

- Kyphosis
- Reduced FVC = each fracture $\downarrow$ FVC by 9%
- Increased mortality rate – associated w hip fxs $\rightarrow$ 25% will die first year after hip fx
- 1/3 of vertebral fxs are painful
- Hip fracture $\rightarrow$ 1/3 long term ECF
What, Me Worry?
Risk Factors for Primary Osteoporosis

- Age
- BMD
- Caucasian or Asian
- Previous Fragility Fracture
- Family Hx
- Low BMI
- Life Style Factors
- Early/Surgical Menopause
Pathophysicsiology

- Osteoclast
- Resorption
- T cell cytokines
- Differentiation of precursors
- RANKL
- RANK
- Osteoblasts
- Osteoprotegerin (OPG)
Postmenopause?
- Estrogen Deficiency
  - RANKL
  - OPG
Estrogen Replacement

- RANKL

- Apoptosis of osteoclasts

- Bone formation $\rightarrow$ stimulating type 1 collagen synthesis by osteoblasts
The four ghosts in Pacman are programmed to act differently: red chases you, pink just tries to position itself in a set way, blue tries to ambush you, orange is random.
Perimenopause

- **Peak Bone mass** → 25-35 yrs
- 5 years **before menopause** → femurs
- 4-8 years after menopause → **accelerated phase** of bone loss → **continuous phase** thereafter
- Accelerated phase → **estrogen def**
- Continuous phase → **inc PTH** because of decreased intestinal Ca absorption and increased urinary Ca excretion
GOSH CHIP!
TELL ME SOMETHING I DON'T KNOW!
Strategies for Osteoporosis Screening

All postmenopausal women

- Women < 65 yrs old
  - No risk factors
  - Clinical risk factors
    - FRAX without BMD
      - Fracture risk ≥ 9.3%*
    - OSTA
      - High risk

- Women ≥ 65 yrs old
  - Measure BMD (T-score)
    - > -1
      - Assess 10-year fracture risk (FRAX)
        - < 20% Major or < 3% Hip
        - ≥ 20% Major or ≥ 3% Hip
      - Diet and lifestyle advice
        - Diet and lifestyle advice
        - Encourage adequate calcium and vitamin D intake, weight-bearing and balance exercises
    - ≤ -1 and ≥ -2.5
    - ≤ -2.5
      - Start appropriate medical treatment and ensure adequate calcium and vitamin D after excluding secondary causes

- History of fragility fracture

Consider repeating BMD at 65 years old or when clinical risk factors develop
Repeat BMD in 2-5 years' time or when clinical risk factors develop

Figure 1
## Indications for BMD Testing (2013)

<table>
<thead>
<tr>
<th>Age</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 and &gt;</td>
<td>Post Menopausal Women &lt; 65</td>
<td>70 and &gt;</td>
</tr>
<tr>
<td>Associated Risk factor for Low bone mass*</td>
<td></td>
<td>&lt; 70 Yrs</td>
</tr>
<tr>
<td>Clinical Risk factors **</td>
<td>during menopausal transition</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>fragility fracture</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>Disease or condition associated with low bone mass or loss</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>medications associated with low bone mass or loss</td>
<td></td>
</tr>
<tr>
<td>Anyone</td>
<td>being considered for pharmacological therapy</td>
<td></td>
</tr>
<tr>
<td>Anyone</td>
<td>being treated, to monitor treatment effect</td>
<td></td>
</tr>
<tr>
<td>Anyone</td>
<td>not receiving therapy in whom e/o bone loss would lead to treatment</td>
<td></td>
</tr>
</tbody>
</table>

*Women discontinuing oestrogen should be considered for bone density testing according to indications listed above.*

**Risk factors for low bone mass**
- Low body weight
- Prior fracture
- High risk medication use
- Disease/condition associated with bone loss.

**Clinical risk factors for**
- Low body weight
- Prior fracture
- High risk medication use
Diagnosis

- Fragility Fracture (regardless of T-score)

  OR

- T-score (lowest value)
I’VE FALLEN AND I CAN’T GET UP!

GOOD
O **T-score**
  O BMD expressed as the number of standard deviations above or below the mean BMD of normal young adults (30 yrs old)

O **Z-score**
  O BMD expressed as the number of standard deviations above or below the mean BMD of adults of the same age and gender

O **Absolute BMD**
  O Actual BMD $\rightarrow \text{g/cm}^2$
  O Used to calculate change over time
T - Score

Normal Bone Mineral Density (> -1.0)

Osteopenia (-1.0 to -2.5)

Osteoporosis (< -2.5)
Facility: 80 years 05.08.1922
147 cm 68 kg White Female
Physician:

AP SPINE BONE DENSITY

Acquired: 25.03.2003 (4.7d)
Analyzed: 25.03.2003 (4.7d)
Printed: 07.04.2003 (4.7d)

Image not for diagnosis
0.75ma: S1ow DP:1 1.2x1.2mm 1.68mm
716555: 413937 275.66:205.32:145.88
XFat = 29.6(1.333)
T-score Significance

- **T-1**
  - 12% Bone Loss
  - 2 fold increase in fx risk

- **T-2**
  - 24% Bone Loss
  - 4 fold increase in fx risk

- **T-3**
  - 36% Bone Loss
  - 8 fold increase in fx risk

At about 30% bone loss (T-2.5) one can see osteopenic changes on radiographs.
National Osteoporosis Foundation
Treatment Guidelines

Treat postmenopausal women and men age 50 y and older who have...

Osteoporosis
- Clinical diagnosis: hip or spine fracture
- DXA diagnosis: T-score -2.5 or less in the spine or hip

T-scores between -1.0 and -2.5 and increased fracture risk

- Use FRAX to estimate 10-y fracture risk
- Treat if risk is
  - ≥ 3% for hip fracture or
  - ≥ 20% for major osteoporotic fractures

Calculation Tool

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   - Age: 50
   - Date of birth: Y: , M: , D:

2. Sex
   - Male
   - Female

3. Weight (kg)
   - 54.43

4. Height (cm)
   - 170.18

5. Previous fracture
   - No
   - Yes

6. Parent fractured hip
   - No
   - Yes

7. Current smoking
   - No
   - Yes

8. Glucocorticoids
   - No
   - Yes

9. Rheumatoid arthritis
   - No
   - Yes

10. Secondary osteoporosis
    - No
    - Yes

11. Alcohol 3 or more units per day
    - No
    - Yes

12. Femoral neck BMD (g/cm²)
    - T-Score: -2
    - Clear
    - Calculate

Weight Conversion

Pounds
- 120
- Convert

Height Conversion

Inches
- 67
- Convert

BMI 18.8
The ten year probability of fracture %
with BMD

- Major osteoporotic: 18
- Hip fracture: 3.7
Treatment

- Goal of treatment → prevention
- For each 1 SD decrement (T score) in BMD risk of fracture increases by a factor of 2 to 3
- Check Vit D status
- Ca x Phos must be >24 to mineralize bone
- IF patient has low Z score must strongly consider secondary etiology for osteoporosis
Conditions that Affect Bone Mass

- Menopause, hypogonadism, prolactinoma
- Hyperparathyroidism
- Hypercalciuria
- Hypercortisolism
- Hyperthyroidism
- Diabetes mellitus, type I
- Paralysis
- Malnutrition - Ca, vit D, protein/calorie, TPN

- Intestinal malabsorption (sprue, Crohn's, etc.)
- Gastrectomy
- Renal insufficiency
- Rheumatoid arthritis
- Multiple myeloma
- Mastocytosis
- Malignancies
- Chronic lung disease
- Alcoholism
Management

- Non-pharm options
  - **Resistance** and **weight bearing** exercise
    - Benefit on skeletal microarchitecture
  - **Fall** reduction
    - Balance programs – yoga and tai chi
    - Withdrawl of **psychotropic** meds
  - Counseling about **cigarette** smoking and excess **EtOH** use
Calcium and Vit D

- Postmenopausal women with osteoporosis
  - Ca 1000 to 1500 mg/day
  - Vit D 600 to 800 IU/day
- Only small reduction in fracture risk
  - Mostly in institutionalized elderly

So what are some good sources of dietary calcium?
Well Absorbed Dietary Sources of Calcium

- Plain low-fat yogurt 8oz $\rightarrow$ 448mg Ca
- Mozzarella 1.5oz $\rightarrow$ 333mg Ca
- 2% Low fat milk 1 cup $\rightarrow$ 293mg Ca
- Calcium fortified OJ $\rightarrow$ 261mg Ca
- Pink Salmon 3.0oz $\rightarrow$ 183mg Ca

Table 3. Widely Available Calcium Supplements.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose</th>
<th>Elemental Calcium Content</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium carbonate</td>
<td>One or two 500-mg tablets taken orally two or three times daily with meals</td>
<td>40</td>
<td>Least expensive and most commonly used supplement; should be taken with meals, since acidity improves absorption; can cause constipation</td>
</tr>
<tr>
<td>Calcium citrate</td>
<td>One or two 950-mg or 1000-mg tablets taken orally two or three times daily</td>
<td>21</td>
<td>Less dependent on acidity for absorption, so it does not need to be taken with meals; may be used with agents for long-term gastric acid suppression</td>
</tr>
<tr>
<td>Calcium gluconate</td>
<td>500, 648, or 972 mg</td>
<td>9</td>
<td>Rarely used for fracture prevention</td>
</tr>
<tr>
<td>Calcium lactate</td>
<td>300 or 325 mg</td>
<td>13</td>
<td>Rarely used for fracture prevention</td>
</tr>
<tr>
<td>Bone meal, oyster shell, dolomite</td>
<td>Varies</td>
<td>30</td>
<td>Primarily contains calcium carbonate but may contain detectable lead and should be avoided during pregnancy</td>
</tr>
</tbody>
</table>
Pharmacologic Therapies

- Antiresorptive
  - Targeting osteoclast-mediated bone resorption
- Anabolic
  - Stimulating osteoblasts to form new bone
<table>
<thead>
<tr>
<th>Drug (Brand)</th>
<th>Dosing</th>
<th>Route</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bisphosphonates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>Treatment: 10 mg once daily or 70 mg once weekly</td>
<td>Oral</td>
<td>Dyspepsia, abdominal pain, musculoskeletal pain</td>
</tr>
<tr>
<td></td>
<td>Prevention: 5 mg once daily or 35 mg once weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronate (Boniva)</td>
<td>Oral: 2.5 mg once daily or 150 mg once a month</td>
<td>Oral, IV</td>
<td>Dyspepsia, back pain, musculoskeletal pain, headache, abdominal pain</td>
</tr>
<tr>
<td></td>
<td>IV: 3 mg every 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risedronate (Actonel, Atelvia)</td>
<td>IR: 5 mg once daily or 35 mg once weekly or 150 mg once a month</td>
<td>Oral</td>
<td>Rash, abdominal pain, dyspepsia, diarrhea, arthralgia</td>
</tr>
<tr>
<td></td>
<td>DR: 35 mg once weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid (Reclast)</td>
<td>5 mg once a year</td>
<td>IV</td>
<td>Acute reaction (flu-like symptoms, fever, myalgia) may occur within 3 days of infusion; hypotension, fatigue, eye inflammation, nausea, vomiting, abdominal pain</td>
</tr>
<tr>
<td><strong>Calcitonin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitonin (Fortical)</td>
<td>200 IU in 1 nostril daily alternating each day</td>
<td>Intranasal</td>
<td>Rhinitis, nasal irritation, dizziness, nasal dryness</td>
</tr>
<tr>
<td>Calcitonin (Miacalcin)</td>
<td>100 IU every other day, 200 IU in 1 nostril daily alternating each day</td>
<td>SC, IM</td>
<td>Injection site reactions, nausea, vomiting, abdominal cramping, flushing</td>
</tr>
<tr>
<td><strong>Selective Estrogen Receptor Modulator</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raloxifene (Evista)</td>
<td>60 mg once daily</td>
<td>Oral</td>
<td>VTE, arthralgia, leg cramps, flu syndrome, peripheral edema, hot flashes</td>
</tr>
<tr>
<td><strong>Parathyroid Hormone Analogue</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teriparatide (Forteo)</td>
<td>20 mcg once daily</td>
<td>SC</td>
<td>Transient hypercalcemia, nausea, rhinitis, arthralgia, pain</td>
</tr>
<tr>
<td>Denosumab (Prolia)</td>
<td>60 mg every 6 months</td>
<td>SC</td>
<td>Dermatitis, rash, mild bone/muscle pain, UTIs</td>
</tr>
</tbody>
</table>

Estrogen Replacement

- RANKL
- Apoptosis of osteoclasts
- Bone formation $\rightarrow$ stimulating type 1 collagen synthesis by osteoblasts
Estrogen and SERMs

- Low dose conjugated estrogens and ultra low dose estradiol
  - Breast ca, CVA, coronary and thrombotic risks
- Raloxifene – FDA approved
  - Decreases risk of vertebral fxs by 30%
  - No effect on nonvertebral or hip fxs
Bisphosphonates

- **Oral** and **IV** forms
- **Majority** of Rx for osteoporosis tx
- Generally **safe**
- Must have **eGFR >**35 ml/min and normal **vitamin D** level (otherwise can have significant hypoCa with BP tx)
- Mild **hypoCa** and **muscle pain**
- **Esophagitis**
- Two rare side effects
  - Atypical femoral neck fractures
  - **Osteonecrosis of the jaw**
Bisphosphonates inhibit osteoclast activity, and promote osteoclast apoptosis.

Bisphosphonates may modulate signaling from osteoblasts to osteoclasts:
- Increased OPG production
- Decreased RANKL expression

Bisphosphonates are released locally during bone resorption.

Bisphosphonates are concentrated under osteoclasts.
HMG-CoA → Mevalonate → Mevalonate phosphotransferase → Phosphomevalonate → Phosphomevalonate kinase → Mevalonate-diphosphate → MevalonatePP decarboxylase → IPP isomerase → IPP ↔ DMAPP → FPP synthase → N-Bisphosphonates

Squalene ← FPP → Farnesylated Proteins

Lanosterol ← GGPP

Zymosterol

Desmosterol

Cholesterol

Geranylgeranylating → Osteoclast Function and Survival
- **Oral Bisphosphonates (BPs)**
  - *Weekly* doses (alendronate and risedronate)
  - *Monthly* doses (ibandronate and risendronate)

- **IV BP**
  - Zolendronate q1 *year*
Fracture Risk Reduction with Alendronate in Women with Osteoporosis: The Fracture Intervention Trial

We conclude that reductions in fracture risk during treatment with alendronate are consistent in women with existing vertebral fractures and those without such fractures but with bone mineral density in the osteoporotic range. Furthermore, reduction in risk is evident early in the course of treatment. This pooled analysis provides a more precise estimate of the antifracture efficacy of alendronate in women with osteoporosis than that in prior reports. (*J Clin Endocrinol Metab* 85: 4118–4124, 2000)
A

Women 70 to 79 Years Old

Patients with Hip Fracture (%)

Month

No. at Risk

Risedronate  3624  3040  2681  2464
Placebo     1821  1526  1339  1210
- Low **adherence** to oral BPs
- Taken with a full glass of water
- **Empty** stomach
- **Up-right** x30 mins after
- Estimated that <40% of patients are still taking them after 1 year
- IV BPs – Zoledronic acid
Once-Yearly Zoledronic Acid for Treatment

ABSTRACT

BACKGROUND
A single infusion of intravenous zoledronic acid decreases bone turnover and improves bone density at 12 months in postmenopausal women with osteoporosis. We assessed the effects of annual infusions of zoledronic acid on fracture risk during a 3-year period.

CONCLUSIONS
A once-yearly infusion of zoledronic acid during a 3-year period significantly reduced the risk of vertebral, hip, and other fractures. (ClinicalTrials.gov number, NCT00049829.)
**D Any Clinical Fracture**

Cumulative Incidence (%) vs Month

- **Zoledronic acid**
- **Placebo**

Hazard ratio, 0.67 (95% CI, 0.58–0.77)
P < 0.001

**E Clinical Vertebral Fracture**

Cumulative Incidence (%) vs Month

- **Zoledronic acid**
- **Placebo**

Hazard ratio, 0.23 (95% CI, 0.14–0.37)
P < 0.001
E  Serum Bone-Specific Alkaline Phosphatase

F  Serum N-Terminal Propeptide
Zolendronic acid can cause flu like sx for up to 3 days after the first infusion in up to 1/3 of patients
  - Rarely after subsequent infusions
  - Give with acetaminophen – reduces by 50%
And now...
Return of our good ol’ friends...
RANK and RANKL

BEST FRIENDS
FOREVER
Denosumab

- Biologic therapy
- Binds RANKL
  - Decreasing differentiation of osteoclasts
- Can be used with low eGFR
- Can, like BPs, cause atypical femur fxs and osteonecrosis of the jaw
CONCLUSIONS
Denosumab given subcutaneously twice yearly for 36 months was associated with a reduction in the risk of vertebral, nonvertebral, and hip fractures in women with osteoporosis. (ClinicalTrials.gov number, NCT00089791.)
Teriparatide (PTH 1-34)

- **Anabolic** agent
  - Increasing bone formation
- **Daily self injection**
  - Approved for up to **2 years**
- After discontinuation – **benefit** is quickly **lost**
  - Should be **followed** by an **antiresorptive** agent
- BBW → **Osteosarcoma**
Teriparatide is amino acid sequence 1-34 of the human PTH molecule.

Chronically elevated PTH leads to bone resorption.

Intermittent exposure to PTH → activate osteoblasts more than osteoclasts.

Net effect of once daily teriparatide is stimulation of new bone formation.
Intermittent PTH ↑
Net bone formation

Sustained PTH ↑
Net bone resorption

- Bone metabolism ↑
- Ca^{2+} reabsorption in kidney ↑
- 1,25-dihydroxyvitamin D synthesis ↑
(increases intestinal Ca^{2+} absorption)

Nature Reviews | Drug Discovery
PTH

Osteocatabolic

↑ RANKL
↓ OPG
↑ Osteoclast Differentiation
↑ Bone Resorption

Osteoanabolic

↑ Osteoblast Differentiation
↓ Apoptosis
↑ Bone Formation

Osteoblast Lineage
Based on what we now know, in patients previously treated with bisphosphonates who suffer hip fractures or who have very low or declining hip BMD, strong consideration should be given to starting TPTD and continuing a potent antiresorptive agent (possibly switching to zoledronic acid or denosumab) to improve hip BMD and strength quickly. Furthermore, in treatment naïve individuals with very severe osteoporosis, such as those with spine and hip fractures, combination therapy with TPTD and denosumab or TPTD followed by combination treatment with a potent bisphosphonate or denosumab should be considered to maximize early increases in BMD throughout the skeleton (Cosman BoneKEy Rep 3, 2014)[1].
CONCLUSIONS

After one year of parathyroid hormone (1–84), densitometric gains appear to be maintained or increased with a lendronate but lost if parathyroid hormone is not followed by an antiresorptive agent. These results have clinical implications for therapeutic choices after the discontinuation of parathyroid hormone.
On the Horizon...

- **Anti-sclerostin antibody** → Romosozumab
- **Sclerostin** – BMP antagonist; binding to LRP5/6 receptors and inhibiting the Wnt signaling pathway → decreased bone formation
- Increased BD more than BP and teriparatide
- Mild injection SEs
- Monthly injections
- On the market 2017...
Wnt Signaling Pathway

Sclerostin and DKK1 inhibit Wnt signaling

Antibodies to sclerostin and DKK1 stimulate Wnt signaling

Kremen → LRP5/6 → ↓ Wnt signaling → ↓ Bone formation

LRP4 → Wnt → Scl → DKK1 → DKK1 Ab

LRP5/6 → ↑ Wnt signaling → ↑ Bone formation

Atypical Fractures

- Strongest part of the femur – subtrochanteric and diaphyseal region
- History (Hx) of prodromal thigh pain, circumferential cortical thickening and cortical stress lesions – precede a complete transverse or oblique fx
- Pathologic mechanism unclear
- Possible that ongoing bisphosphonate therapy blocks targeted remodeling of cracks

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68
### Table 1. Risk of Atypical Femoral Fracture Associated with Bisphosphonate Use during the 3 Years (2005–2008) Preceding the Fracture.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Women</th>
<th>Cases of Atypical Fracture</th>
<th>Age-Adjusted Relative Risk (95% CI)</th>
<th>Age-Adjusted Absolute Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Atypical Fracture Cases</td>
<td>Crude Incidence no./10,000 patient-yr</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1,437,820</td>
<td>13</td>
<td>0.09</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>Ever</td>
<td>83,311</td>
<td>46</td>
<td>5.5</td>
<td>47.3 (25.6–87.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0005 (0.0004–0.0007)</td>
</tr>
<tr>
<td><strong>Duration of use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 yr</td>
<td>15,672</td>
<td>3</td>
<td>1.9</td>
<td>18.4 (5.3–64.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0002 (0.0000–0.0004)</td>
</tr>
<tr>
<td>1.0–1.9 yr</td>
<td>21,406</td>
<td>4</td>
<td>1.9</td>
<td>17.0 (5.7–50.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0002 (0.0000–0.0004)</td>
</tr>
<tr>
<td>≥2.0 yr</td>
<td>46,233</td>
<td>39</td>
<td>8.4</td>
<td>67.0 (35.8–125.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0008 (0.0006–0.0011)</td>
</tr>
<tr>
<td><strong>Time since last use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1.0 yr</td>
<td>83,311</td>
<td>42</td>
<td>5.0</td>
<td>42.9 (22.9–80.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0005 (0.0004–0.0007)</td>
</tr>
<tr>
<td>1.0–1.9 yr</td>
<td>70,036</td>
<td>1</td>
<td>0.1</td>
<td>3.5 (1.0–11.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001 (0.0000–0.0000)</td>
</tr>
<tr>
<td>≥2.0 yr</td>
<td>75,583</td>
<td>3</td>
<td>0.4</td>
<td>3.2 (1.0–10.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001 (0.0000–0.0001)</td>
</tr>
</tbody>
</table>

* CI denotes confidence interval.
Osteonecrosis of the jaw

Very low incidence 0.001% to 0.01%

General population <0.001%

Higher among patients with cancer

Taking higher doses of BPs or Denosumab

Glucocorticoids and immunosuppressives may increase risk

Prevention – stabilization of oral disease prior to BP use, good oral hygiene


70
Drug Holiday

- Temporary discontinuation for up to 5 years
- **Benefits** are generally retained for up to this amount of time
- Holiday only in those who are considered low risk
  - BMD and vertebral fx status
- Reinitiate tx no longer than 5 yrs after dc
Conclusions  Women who discontinued alendronate after 5 years showed a moderate decline in BMD and a gradual rise in biochemical markers but no higher fracture risk other than for clinical vertebral fractures compared with those who continued alendronate. These results suggest that for many women, discontinuation of alendronate for up to 5 years does not appear to significantly increase fracture risk. However, women at very high risk of clinical vertebral fractures may benefit by continuing beyond 5 years.

Trial Registration  clinicaltrials.gov Identifier: NCT 00398931

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Author Affiliations and Members of the FLEX Research Group are listed at the end of this article.

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Summary

- Osteoporosis and fractures are common
- Phases of bone loss in menopause
  - Accelerated and Continuous
- Pathophysiology players in the game of osteoporosis
  - RANKL and RANK
  - OPG
  - RANKL/OPG ratios
  - Osteoblasts and Osteoclasts
  - New kid Sclerostin
- When to treat
  - T score of -2.5 or less,
  - hx of vertebral or hip fracture
  - FRAX score indicates increased fracture risk
- Non Pharm therapies
  - Ca and Vit D
- Anabolic and Anti-resorptive therapies
- Biologic therapies
- Significant side effects
- Possibility of drug holidays
Getting old isn’t all bad...

With Age comes skills
It’s called MultiTasking
I CAN LAUGH, COUGH, SNEEZE, AND PEE ALL AT THE SAME TIME.
Special thanks to Dr. Robert Hawkins...
APPENDIX
Calcium supplement intake and risk of cardiovascular disease in women.

Paik JM, Curhan GC, Sun Q, Rexrode KM, Manson JE, Rimm EB, Taylor EN.

Abstract

Some recent reports suggest that calcium supplement use may increase risk of cardiovascular disease. In a prospective cohort study of 74,245 women in the Nurses' Health Study with 24 years of follow-up, we found no independent associations between supplemental calcium intake and risk of incident coronary heart disease (CHD) and stroke.

INTRODUCTION: Some recent reports suggest that calcium supplements may increase cardiovascular disease (CVD) risk. The objective was to examine the independent associations between calcium supplement use and risk of CVD.

METHODS: We conducted a prospective cohort study of supplemental calcium use and incident CVD in 74,245 women in the Nurses' Health Study (1984-2008) free of CVD and cancer at baseline. Calcium supplement intake was assessed every 4 years. Outcomes were incident CHD (nonfatal or fatal MI) and stroke (ischemic or hemorrhagic), confirmed by medical record review.

RESULTS: During 24 years of follow-up, 4,565 cardiovascular events occurred (2,709 CHD and 1,856 strokes). At baseline, women who took calcium supplements had higher levels of physical activity, smoked less, and had lower trans fat intake compared with those who did not take calcium supplements. After multivariable adjustment for age, body mass index, dietary calcium, vitamin D intake, and other CVD risk factors, the relative risk of CVD for women taking >1,000 mg/day of calcium supplements compared with none was 0.82 (95% confidence interval [CI] 0.74 to 0.92; p for trend <0.001). For women taking >1,000 mg/day of calcium supplements compared with none, the multivariable-adjusted relative risk for CHD was 0.71 (0.61 to 0.83; p for trend < 0.001) and for stroke was 1.03 (0.87 to 1.21; p for trend = 0.61). The relative risks were similar in analyses limited to non-smokers, women without hypertension, and women who had regular physical exams.

CONCLUSIONS: Our findings do not support the hypothesis that calcium supplement intake increases CVD risk in women.
Activated T lymphocytes
Activated synovial fibroblasts

CFU-GM
M-CSF
Preosteoclast

Multinucleated osteoclast

Osteoblasts or bone marrow stromal cells
Bone

Pro-resorptive and calcitropic factors
1,25(OH)₂ vitamin D₃, PTH, PTHrP, PGE₂, IL-1, IL-6, TNF, prolactin, corticosteroids, oncostatin M, LIF
Anabolic or anti-resorptive factors: Oestrogens, calcitonin, BMP 2/4, TGF-β, TPO, IL-17, PDGF, calcium.
<table>
<thead>
<tr>
<th>Type of Food</th>
<th>Serving Size</th>
<th>Elemental Calcium per Serving</th>
<th>Calories per Serving</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy products</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plain low-fat yogurt</td>
<td>8.0 oz</td>
<td>448</td>
<td>154</td>
</tr>
<tr>
<td>Low-fat yogurt with fruit</td>
<td>8.0 oz</td>
<td>384</td>
<td>238</td>
</tr>
<tr>
<td>Mozzarella, part skim milk</td>
<td>1.5 oz</td>
<td>333</td>
<td>108</td>
</tr>
<tr>
<td>Cheddar cheese</td>
<td>1.5 oz</td>
<td>307</td>
<td>171</td>
</tr>
<tr>
<td>2% Low-fat milk</td>
<td>1 cup</td>
<td>293</td>
<td>122</td>
</tr>
<tr>
<td>Low-fat cottage cheese</td>
<td>1 cup</td>
<td>206</td>
<td>194</td>
</tr>
<tr>
<td>Fruits and vegetables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium-fortified orange juice</td>
<td>6.0 oz</td>
<td>261</td>
<td>88</td>
</tr>
<tr>
<td>Raw kale</td>
<td>1 cup</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>Raw bok choy</td>
<td>1 cup</td>
<td>74</td>
<td>9</td>
</tr>
<tr>
<td>Raw broccoli</td>
<td>1 cup</td>
<td>43</td>
<td>31</td>
</tr>
<tr>
<td>Canned fish</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sardines</td>
<td>3.0 oz</td>
<td>325</td>
<td>177</td>
</tr>
<tr>
<td>Pink salmon</td>
<td>3.0 oz</td>
<td>183</td>
<td>110</td>
</tr>
<tr>
<td>Grains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fortified, ready-to-eat cereals</td>
<td>1 cup</td>
<td>100–1333</td>
<td>100–160</td>
</tr>
<tr>
<td>Fortified, cooked oat cereals</td>
<td>1 cup</td>
<td>187</td>
<td>159</td>
</tr>
<tr>
<td>Commercially prepared white or wheat bread</td>
<td>1 slice</td>
<td>30–73</td>
<td>69–74</td>
</tr>
</tbody>
</table>

* These foods contain low levels of oxalic and phytic acid. Data are from the National Nutrient Database for Standard Reference of the U.S. Department of Agriculture.7

Figure 4: Bisphosphonate Structure—Bisphosphonates are structurally related to the mineralized bone matrix component pyrophosphate and belong to two general classes. The more potent nitrogen-containing bisphosphonates possess one or more nitrogen atoms in their variable side chains around the central carbon atom. Adapted from Reszka et al.[38]
Nitrogen-Containing BPs

mevalonate

dimethylallyl diphosphate

isopentenyl diphosphate (IPP)

FPP synthase

cholesterol

dimethylallyl diphosphate (FPP)

farnesyl diphtosphate

farnesylated proteins

geranylgeranyl diphtosphate (GGPP)

geranylgeranylated proteins

proteins required for osteoclast function and survival

metabolites induce osteoclast apoptosis

Simple BPs
HMG-CoA → Mevalonate → Geranylpyrophosphate + IPP

- NBP inhibits FPP synthase, thereby blocking the prenylation of small signaling proteins required for cell function and survival.

- Accumulation of IPP, which stimulates the expansion of Vγ9Vδ2 T cells.

FPP synthase

GGPP synthase

Ras

Rho
### TABLE 3. RR of alendronate vs. placebo in combined osteoporotic group (existing vertebral fracture at baseline or femoral neck T score of −2.5 or less)

<table>
<thead>
<tr>
<th>Fracture class</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologic vertebral</td>
<td>0.52 (0.42, 0.66)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multiple vertebral (radiologic)</td>
<td>0.13 (0.07, 0.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical vertebral</td>
<td>0.55 (0.36, 0.82)</td>
<td>0.003</td>
</tr>
<tr>
<td>Any clinical</td>
<td>0.70 (0.59, 0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonvertebral</td>
<td>0.73 (0.61, 0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonvertebral (osteoporotic)</td>
<td>0.64 (0.51, 0.80)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hip</td>
<td>0.47 (0.26, 0.79)</td>
<td>0.005</td>
</tr>
<tr>
<td>Wrist</td>
<td>0.70 (0.49, 0.98)</td>
<td>0.038</td>
</tr>
</tbody>
</table>

### TABLE 4. Number needed to treat with alendronate for 5 yr to prevent selected types of fracture

<table>
<thead>
<tr>
<th>Fracture class</th>
<th>Women with existing vertebral fracture (Vertebral Fracture Arm)</th>
<th>Women without vertebral fracture and T score &lt; −2.5 (Clinical Fracture Arm/low BMD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any radiologic vertebral</td>
<td>8</td>
<td>29</td>
</tr>
<tr>
<td>Any clinical</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Any nonvertebral</td>
<td>21</td>
<td>12</td>
</tr>
<tr>
<td>Hip</td>
<td>46</td>
<td>66</td>
</tr>
</tbody>
</table>
Case 1

- 38 year old female with family history of mother with osteoporosis (mother just had hip fracture at age 68)
- She does not have prior steroid use, PPI use, rheumatoid arthritis, tobacco or alcohol
- She had fracture of clavicle during high impact motor vehicle accident
- DEXA scan was done after she requested it when her mother had recent fracture.
- Z score was -2.7
- What is the next step?
O Check for causes of low bone density
  O Check routine labs including CMP and 25-OH Vit D.
  O Check urinary calcium excretion
    O Can use low dose hydrochlorothiazide if high
  O Check for problems with absorption
    O Such as IBD or Celiac Disease
  O Consider 24 hour urine cortisol if cushinoid
Case 2

- 41 year old premenopausal female with history of SLE who has been on long courses of steroids and has had hip fracture after fall from standing position a year ago. She has chronically been on PPI for GI prophylaxis.
- She does not have family history of fracture/osteoporosis or rheumatoid arthritis
- Denies EtOH or tobacco use
- Labs: creatinine 0.9, Calcium normal, 25-OH Vit D 15
- DEXA scan with Z score of -3.6 at spine and -3.4 at hip.
- What are the next steps?
O Replace Vitamin D
  O 50,000 units weekly for 8-12 weeks, then 1000-2000 units/day
O Advise Calcium 1000-1400 mg daily (supplement + diet)
O Teriparatide may be worth considering as initial treatment to increase bone density given several fractures
Case 3

- 82 year old male with end stage kidney disease with osteoporosis with T score of -3.2 at lumbar spine and -2.9 at femoral neck.
- He has kyphosis with vertebral compression fractures on x-ray of thoracic spine.
- Estimated GFR 22, 25-OH-Vit D 40, calcium normal, PTH mildly elevated.
- What is the treatment choice?
- Denosumab (Prolia)
- Cannot use bisphosphonates given low eGFR.
- Avoid Teriparatide given elevated PTH
- For men, in general would be worth to check testosterone level and consider replacement therapy.