Calcium, Vitamin D and Bisphosphonates:

Benefits, Risks and Drug Holiday

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Michael McClung, MD
2013

Calcium – YES or NO?

Calcium – Bad News!!

USPSTF Says No to Vitamin D, Calcium for Older Women
ABC News Feb 25, 2013

No Vitamin D and Calcium for Older Bones.
A government task force formally recommended on Monday that healthy postmenopausal women avoid taking low daily doses of vitamin D and calcium to ward off bone fractures.
NY Times Feb 25, 2013

Calcium and Skeletal Health

- Adequate calcium intake is important
  - during years of growth (especially adolescence) optimizes stature and peak bone mass ??
  - premenopausal women preserves bone mass ??
  - early postmenopausal women minimal effect on bone mass
  - older men and women (with vitamin D) may slow bone loss and prevent fractures

Calcium Intake and Bone Health

- Fuller Albright demonstrated that estrogen deficiency and menopause was associated with negative calcium balance, correctable by estrogen therapy.
- Calcium intake of at least 1500 mg/day required to normalize negative calcium balance in postmenopausal women.
- Increasing calcium intake by 500 mg daily reduced bone loss in calcium deficient adults but not in those with moderate or high calcium intake.
Calcium Intake and PTH Suppression

- Very low calcium intake associated with increased risk of hip fracture

Calcium Intake and Bone Health

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Calcium Supplements May Increase Cardiovascular Risk

- Re-analysis of WHI Calcium Cohort suggested increased CV risk with calcium supplements
  - After an average of 11 years, calcium and vitamin D supplementation did not alter CVD or all-cause mortality.

Calcium Intake and Supplements

- Updated recommended intake: Target - 1200 mg daily
  - Supported by NOF and AACE
  - The USPSTF recommends against daily supplementation with ...1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women.
    - (Grade D recommendation)

Vitamin D – YES or NO?

- Low vitamin D levels associated with increased incidence of breast and prostate cancer, diabetes, multiple sclerosis, congestive heart failure, myocardial infarction in men, autoimmune disorders, poor pregnancy outcomes and other illnesses.
  - Prospective trials and meta-analyses confirm salutary effects of vitamin D supplementation
    - reduced falls (49% over 3 months)
    - decreased fracture risk (35% over 5 years)
    - decreased mortality

Vitamin D Deficiency (<20 ng/ml)

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**Vitamin D and Bone Health**

Very low vitamin D levels (<10 ng/ml) associated with increased bone loss and falls in older adults

Sato Y et al. Stroke 2001;326:1673-7

Treating vitamin D deficient older adults with 800 IU vitamin D3 daily reduces risk of falls and fracture


Serum levels >50 ng/ml may be associated with increased risk of cancer and death

Autier P and Gandi S. Arch Intern Med, 2007;167:1730-1737


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**Vitamin D and Mortality**

**All-Cause Mortality**

**Cancer Mortality**

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**Vitamin D Intake - Guidelines**

- IOM recommendation: 600-800 IU of vitamin D3/day to achieve a serum level of 20 ng/ml
- The Endocrine Society recommendation: Daily intake 600-2000 IU daily with target of 30 ng/ml
- Other recommendations
  - NOF: 800-1000 IU daily
  - Osteoporosis Canada and IOF: 800-2000 IU daily
  - 1000 IU daily increases serum 25-OH vitamin D by about 10 ng/ml


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**Calcium & Vitamin D: What Now?**

- Calcium and probably vitamin D are threshold nutrients
  - Too little is not good
  - Too much is not better and may be harmful
  - MODERATION is the key!

So, reasonable recommendations for daily intake

Calcium: 800-1200 mg/day
Vitamin D: 800-2000 IU daily

?? If patients with inflammatory disorders would benefit from higher intakes

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**Bisphosphonates: Skeletal Benefits**

1. Effective protection from fractures
   - Vertebral fracture by 60-70%
   - in GIO – 70% reduction by 1 year
   - Multiple vertebral fractures by 75-96%
   - Hip fracture by 40-50%
   - Non-vertebral fracture by 20-35%

2. In general are well tolerated
3. In clinical trials, have been very safe


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**Fracture Protection with Bisphosphonate Therapy Occurs Quickly**

Vertebral fracture risk reduced within 6-12 months

Nonvertebral Fracture

Hip Fracture

Post-hoc Analyses of Pooled Clinical Trial Data

Harrington, Calcif Tissue Int 2004;74:123
Fracture Protection Persists

- Fracture protection persists but does not improve with long term therapy

Vertebral Fracture Risk over Time

<table>
<thead>
<tr>
<th>Years 0-3</th>
<th>Years 4-5</th>
<th>Years 5-7</th>
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<tr>
<td>Placebo</td>
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<td>3.8%</td>
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</tbody>
</table>

Subjects switched to risedronate 5 mg at end of year 5

Mellstrom DO et al. Calcif Tissue Int. 2004;75:462-8

Bisphosphonates: Side Effects

Upper GI Intolerance
- not observed in clinical trials
- rarely severe but limits acceptance of therapy

Acute phase reaction
- IV or high dose oral therapy

Bone and muscle pain
- not observed in clinical trials
- unknown incidence or cause

Inflammatory eye problems
- uveitis, iritis

Renal impairment/failure with IV therapy

Anaphylactic reaction

Bisphosphonates: Major Safety Concerns

Atrial fibrillation associated with hospitalization (1)
- Observed in one of two HORIZON trials
- No association with timing of infusion
- No association with other cardiovascular outcomes

FDA concluded that evidence for link between bisphosphonate use and atrial fibrillation is not established (2)


Esophageal cancer with oral bisphosphonates
- A series of cases of patients with esophageal cancer and prior oral bisphosphonate use was reported (1)
- Most observational studies observed no or decreased risk (2,3)
- One study noted an increased risk in patients who had 10 or more prescriptions of oral bisphosphonates or who had taken the drugs over 3 years. Absolute risk would be 1/1000 after treatment for 5 years (4)
- FDA has not concluded that taking an oral bisphosphonate drug increases the risk of esophageal cancer.


Other Potential “Benefits” of Bisphosphonate Therapy

- Decreased risk of breast, colorectal and gastric cancer
- Decreased risk of stroke (HR = 0.79; 95% CI = 0.86-0.99)
- Decreased risk of MI (HR = 0.35; 95% CI = 0.14-0.84)
- Decreased overall mortality (10-28%)


Email me for list of 10 references
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Bisphosphonates: Concerns about Safety with Long Term Use

Potent inhibitor of bone remodeling with long skeletal half life

- Fracture healing
  - No evidence of impaired fracture healing, even when IV therapy given soon after hip fracture

- Osteonecrosis of the jaw
  - Incidence 1:10,000-1:250,000 with oral drugs
  - Link with osteoporosis doses of bisphosphonates is unproven
  - Minimal evidence of increasing risk with long-term therapy

1. Khoshla S et al. J Bone Miner Res. 2007;22;1478-1491
Atypical Femoral Fracture and Long-term Bisphosphonate Therapy

Increase in absolute risk of 5 cases per 10,000 patient-years (95% CI, 4 to 7)
Duration of use influenced the risk (odds ratio per 100 daily doses, 1.3; 95% CI, 1.1 to 1.6)
After drug withdrawal, the risk diminished by 70% per year since the last use (odds ratio, 0.28; 95% CI, 0.21 to 0.38)

Dell RM et al. J Bone Miner Res. 2012;27:2544-50

Atypical Femoral Fracture and Long-term Bisphosphonate Therapy

Duration-dependent risk of AFF:
1.78/100,000 patient-years in first 2 yr
113/100,000 patient-years in years 8-9.9

Rapid decrease in risk when treatment is stopped

R Dell: personal communication

Atypical Femoral Fracture: Management Tips

- At least 70% of patients have prodomal thigh pain weeks to months before complete fracture occurs
- Periosteal stress reaction may be evident on DXA scan even in patients without symptoms
- In patients in therapy for 3 years or more,
  - counsel to report new thigh pain
  - consider extending DXA scan further down the femoral shaft


Bisphosphonates: Good vs Bad - Risk-Benefit

- Substantial fracture protection benefit when high risk patients are treated
- Fracture protection occurs quickly (weeks-months) and persists but does not get better with long term therapy
- There is a duration-dependent risk of AFF
  - Risk is minimal during first years of therapy
  - Risk decreases quickly when treatment is stopped
- Overall risk:benefit ratio is very favorable out to 10 years – especially during first 5 years

Why Stop Bisphosphonate Therapy for a “Drug Holiday”?

- Therapy loses effect with long term therapy - NO
- Risks increase with long duration of treatment
  - YES only for atypical femoral fracture
  - Benefit far outweighs risk during first 10 years of treatment

Why Stop Bisphosphonate Therapy for a “Drug Holiday”?

- Treatment effect persists after stopping treatment
  - Appears to be true for at least 1 year after stopping risendronate and 2-3 years after stopping alendronate or zoledronic acid

Watts NB, McClung MR et al. Osteoporos Int. 2006;17:355-72
Watts NB, McClung MR et al. Osteoporos Int. 2007;18:1609-22
Clinical Vertebral Fractures in the FLEX Study

Cumulative Incidence of Fractures (%)

Years Since FIT

ALN/PLB

ALN/ALN

ALN 5 years → Placebo 5 years

Alendronate 10 years

Risk reduction of 55%

P = 0.013

2.5%

5.4%

RR

55%

P = 0.013


Rationale for Stopping Bisphosphonate Therapy After 3-5 Years in Modest Risk Patients

After 3-5 years of bisphosphonate therapy:

• stopping treatment for 1-2 years results in
  • reduction in risk of atypical femoral fracture
  • without sacrificing fracture protection

• Therefore, stopping bisphosphonate therapy after 3-5 years for an interval of at least 1-2 years is justified in patients at low or modest risk of fracture


Rationale for NOT Stopping Bisphosphonate Therapy After 3-5 Years in High Risk Patients

After 3-5 years of bisphosphonate therapy:

• stopping treatment for 1-3 additional years results in
  • increased risk of vertebral (0.5-1%/year) and non-vertebral fracture (1-2%/year) in patients with osteoporosis (by FN BMD) or prior vertebral fracture

• Therefore, continuing bisphosphonate therapy after 3-5 years for an interval of up to 10 years is justified in patients still at high risk of spine fracture
  • e.g., >75, T-score <-2.5, multiple vertebral fractures


Duration of Bisphosphonate Therapy

• After 10 years, we have no data to guide clinical decisions.

• In my practice, a drug holiday is recommended to all patients who have been treated for 10 years or longer unless they have experienced a spine or hip fracture within the past 3 years.

McClung - Personal opinion 2013

Operationalizing a “Drug Holiday”

• Duration of “drug holiday”
  • 1 year after risedronate therapy
  • 2-3 years after alendronate or zoledronic acid therapy

• Do not use other potent anti-resorptive agents during the “holiday”

• Re-starting therapy:
  • BMD and bone markers may not be helpful

• My approach: re-evaluate indications for therapy at end of “holiday”. If patient meets criteria for therapy, re-start a treatment


Conclusions

• Calcium and vitamin D
  • too little is not good
  • too much may be bad

• Bisphosphonates
  • Benefit/risk is very favorable
    • in patients at high risk for fracture

• “Drug holiday”
  • not required
  • primarily because of sustained efficacy rather than for safety concerns

Thank you

Working to prevent Bone Attacks

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