Rethinking an Old Problem: Emerging New Developments in Osteoporosis Diagnosis & Treatment

Deborah M. Kado, MD, MS
Professor, UCSD School of Medicine
Departments of Family Medicine & Public Health and Medicine
Director, UCSD Osteoporosis Program, Division of Endocrinology
Disclosures

- Amgen
- Ultragenyx
- UpToDate Royalties
Overview

• Osteoporosis: putting it into perspective

• Diagnosis
  • Traditional DXA – how well does it do in predicting fracture
  • Trabecular Bone Score (TBS)
  • Biomechanical CT scans

• Updates on calcium and vitamin D supplementation

• New FDA approved treatments
  • Abaloparatide
  • Romosozumab

• Geriatrician’s perspective on osteoporosis diagnosis and treatment
Putting Osteoporosis into Perspective: What is it?

- A skeletal disorder characterized by
  - Compromised bone strength predisposing to
  - An increased risk of fracture

- Bone strength reflects integration of two main features:
  - Bone density
  - Bone quality
Putting Osteoporosis in Perspective

- Osteoporotic fractures are common
- 50% of osteoporosis related repeat bone breaks in older adults can be prevented


Putting Osteoporosis in Perspective

- Of the 300,000 hip fractures each year
  - 50% never regain their previous functional capacity
  - 25% end up in nursing homes
  - 25% die within one year

- Vertebral fractures are the most common type of osteoporotic fracture
  - Each fracture causes worsening kyphosis by about 4 degrees
  - Vertebral fractures associated with earlier mortality, especially from pulmonary causes

*Healthcare Cost and Utilization Project, 2012; Kado et al, J Bone Miner Res 2013*
Vertebral fractures and bone density loss are markers of unsuccessful aging, or at least a risk factor for earlier mortality.

**Age-standardized Mortality by Number of Vertebral Fractures**

- Number of Vertebral Fractures: 1, 2, 3, 4, ≥5
- Mortality/1000 woman-years: 0, 5, 10, 15, 20
- p for trend < 0.0001

**Age-adjusted mortality by quartiles of bone loss**

- Quartiles of hip bone loss (%): < -0.29, (-0.29) - 0.49, 0.50 - 1.33, > 1.33
- Mortality/1000 woman-years: 0, 5, 10, 15, 20, 25, 30, 35, 40
- p for trend < 0.0001

Hyperkyphosis also a risk factor for earlier mortality, and mortality due to pulmonary causes in particular

Putting Osteoporosis in Perspective

- Osteoporosis one of the top 10 most costly chronic conditions to Medicare in 2010
  - $30,000 per patient for hip fracture
  - $11,300 for non-vertebral fractures
  - $8,380 for vertebral fractures

- What about men?
  - About 20-25% of hip fractures occur in men
  - Men generally have higher rates of fracture related mortality

*Singer AJ et al, Mayo Clinic Proceedings, 2015; Tosteson A et al, Osteoporos Int 2008*
Putting Osteoporosis in Perspective

Osteoporotic fractures are a highly treatable disease, and yet….

“I stopped taking the medicine because I prefer the original disease to the side effects”
Putting Osteoporosis in Perspective:

Gaps and Solutions in Bone Health

• Diagnosis
  – Shortcomings
  – New diagnostic tools available

• Treatments
  – Revisiting Calcium/Vitamin D supplements
  – New drugs

• Fall prevention
Diagnostic Tests: DXA Scan: Clinical gold standard of diagnosis

• Derived from a 2D image
• Low radiation exposure
• Multiple studies confirm that fracture risk increases as DXA BMD decreases
• The WHO definition of osteoporosis as a T-score of $< -2.5$ was not intended to be used to make treatment decisions

*Cummings et al, JAMA 2002*
Diagnosis: DXA Scan – Gold standard, but how well does it perform?

Prevalence of fractures by osteoporosis risk categories

Percentage of all non-vertebral fractures

Women

Men

Above -1 (Normal)  -1 to -2.5 (Osteopenia) -2.5 or below (Osteoporosis)

Schuit SCE et al, Bone 2004
Case Studies from Osteoporosis Clinic

Case #1

- 59 year old female with a history of hypothyroidism
- At age 55, two rib fractures and history of right ankle fracture when hiking
- At age 57, T3, T4, T7, T9, T10, T11 vertebral fractures with minimal trauma
- No family history of osteoporosis
- DXA 6/15/15 (age 56)
  - Lumbar spine T-score -1.3
  - Left FN T-score -1.1
- At age 59, T8 acute vertebral fracture and presents to my clinic for a second opinion
Case Studies from Osteoporosis Clinic
Case #2

- 57 year old female with a history of hypothyroidism intolerant of oral bisphosphonate prescribed by PMD
- History of finger fracture from playing softball as a teenager, no previous other fractures
- Mother treated with alendronate, never fractured, died at age 74 of leukemia
- DXA Scan 12/2017 GE Lunar
  - Spine T-score -2.9
  - Left FN T-score -2.4
Trabecular Bone Score (TBS)
What is it?

- TBS is a gray-level textural measurement derived from spine DXA images
- Is a validated measure that predicts fracture independently from standard BMD measurements
- TBS can enhance fracture prediction when used in conjunction with FRAX
- Downside: Though FDA approved, not reimbursable through insurance

McCloskey et al, J Bone Miner Res 2015
Trabecular Bone Score (TBS)

Silva et al, J Bone Miner Res 2014
Case Studies from Osteoporosis Clinic
Case #1: 57 yr old with multiple spine fractures

- Secondary work up for osteoporosis returned back unrevealing
- DXA 6/19/17
  - Lumbar spine T-score -0.6
  - Left FN T-score -0.8
  - Trabecular bone score 1.24 and T-score -2.5
- Treatment: IV Reclast given at age 58
Case Studies from Osteoporosis Clinic
Case #2: BMD diagnosed osteoporosis & no fractures

- DXA Scan 12/2017 GE Lunar Scripps
  - Spine L1-L4 T-score -2.9
  - Left FN T-score -2.4

- DXA Scan 06/2018 GE Lunar UCSD
  - Spine L1-L4 T-score -2.9
  - Left FN T-score -2.3
  - TBS score 1.44, T-score -0.5

- FRAX Score
  - Any major osteoporotic fracture 9.2%
  - Hip fracture 1.5%

- FRAX Score adjusted for TBS
  - Any major osteoporotic fracture 7.5%
  - Hip fracture 0.8%
Trabecular Bone Score (TBS) Summary of Evidence

- Meta-analysis of 14 prospective population-based cohorts
  - Does TBS predict fractures independently of FRAX
  - Assessed combined performance of FRAX and TBS in predicting fractures

- Individual-level data of 17,809 men and women, mean age 72 (range 66-77), followed for an average of 6.1 years for hip fracture and major osteoporotic fracture (MOF)

- Integrated into international guidelines from the IOF and ISCD as a validated fracture risk factor

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>TBS only</th>
<th>FRAX + BMD</th>
<th>FRAX + BMD + TBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip</td>
<td>1.44 (1.28-1.62)</td>
<td>2.31 (2.07-2.57)</td>
<td>3.98 (2.90-5.45)</td>
</tr>
<tr>
<td>MOF</td>
<td>1.42 (1.33-1.53)</td>
<td>1.44 (1.33-1.52)</td>
<td>1.48 (1.38-1.58)</td>
</tr>
</tbody>
</table>

McCloskey E et al, J Bone Miner Res 2015
Biomechanical CT (BCT)

- Considers both bone strength and BMD
- Can use abdominal or pelvic CT scans with or without contrast enhancement
- Creates an engineering finite element model of
  - Femur
  - Spine
- Virtually fractures the bone to measure its breaking strength for simulated sideways fall and identifies fragile bone strength
- Also provides DXA-equivalent measurement of hip BMD and T-scores for identifying BMD-defined osteoporosis

FEA-derived virtual stress testing: both patients tested negative for hip osteoporosis, but top patient tested positive for fragile bone strength (Femoral strength < 3000 for women and <3500 for men)
Biomechanical CT (BCT)

- The Fracture, Osteoporosis, and CT Utilization Study (FOCUS)
  - 111,694 women and men >65 years of age from Kaiser eligible, with prior hip CT scan and DXA within 3 years of the CT
  - Compared those with hip fracture (n = 1959) with randomly selected sex-stratified controls (n = 1979)

- Bone strength predicted hip fracture independent of hip BMD

- Higher sensitivity for BCT than traditional DXA

<table>
<thead>
<tr>
<th>Bone Measure</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCT Hip BMD</td>
<td>3.7 (2.7-5.1)</td>
<td>4.0 (2.4-6.6)</td>
</tr>
<tr>
<td>BCT Femoral Strength</td>
<td>3.4 (2.5-4.6)</td>
<td>4.1 (2.5-6.8)</td>
</tr>
<tr>
<td>BCT Hip BMD and FS</td>
<td>3.9 (2.8-5.4)</td>
<td>4.8 (2.6-9.0)</td>
</tr>
<tr>
<td>Hip DXA</td>
<td>2.9 (2.1-4.0)</td>
<td>3.3 (2.0-5.3)</td>
</tr>
</tbody>
</table>
Biomechanical CT (BCT)

- Validated measure in several population-based cohort studies
- MrOS Study - Case cohort design of men with hip fractures (n = 40) and random sample (n = 210) from 3,549 men >65 years of age
- Average follow-up of 5.6 years
- Age-adjusted hip fracture risk
  - 8.0 (2.6-24.3) for FN
  - 4.6 (2.6-8.3) for DXA hip BMD

Orwoll et al, J Bone Miner Res 2009
Biomechanical CT (BCT)

- Fracture Risk Assessment considers both
  - Bone Strength
  - BMD

- In 2007, 24.2 million abdominal CT scans were done in the U.S.

- In 2016, about 10% of all Kaiser patients >65 years had an abdominal CT scan

- Between 2006-09, DXA screening rates in the Medicare population were
  - 9.5% for women
  - 1.7% for men

Adams A et al, J Bone Miner Res 2018
Summary of Diagnostic Imaging

- Imaging
  - Routine DXA
    - Widely available in U.S.
    - Reimbursable by insurance
  - Trabecular Bone Score
    - Limited to specialty centers. UCSD is only site in San Diego area.
    - Not reimbursable by insurance
    - Included in FRAX
  - Biomechanical CT scan
    - Newer technology
    - Opportunistic in that can analyze abdominal CT scans done for other reasons
    - Incorporates a measure of bone strength so attractive
    - Medicare Insurance coverage in the U.S. just approved fall 2019
Osteoporosis Treatments: Starting with calcium and vitamin D

2018 USPSTF published recommendations

"The USPSTF found adequate evidence that supplementation with vitamin D and calcium increases the incidence of kidney stones."

Ref: JAMA 2018

<table>
<thead>
<tr>
<th>Population</th>
<th>USPSTF recommendation grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN AND PREMENOPAUSAL WOMEN</td>
<td>Vitamin D, calcium, or combined supplements</td>
</tr>
<tr>
<td></td>
<td>There is insufficient evidence to assess the balance of benefits and harms.</td>
</tr>
<tr>
<td>POSTMENOPAUSAL WOMEN</td>
<td>Vitamin D (&lt;400 IU) and calcium (&lt;1000 mg)</td>
</tr>
<tr>
<td></td>
<td>Not recommended.</td>
</tr>
<tr>
<td></td>
<td>Vitamin D (&gt;400 IU) and calcium (&gt;1000 mg)</td>
</tr>
<tr>
<td></td>
<td>There is insufficient evidence to assess the balance of benefits and harms.</td>
</tr>
</tbody>
</table>

These recommendations apply to community-dwelling adults without osteoporosis, vitamin D deficiency, or history of fractures.
Calcium: What is one to do? Example of when experts don’t agree

• Calcium supplementation still widely recommended in the U.S., though the data are controversial

• Older men & women recommended intake: 1,000-1,200 mg/day for bone health and fracture prevention

• Average dietary intake in Western countries: 700-900 mg/day

• 30-50% of older women take calcium supplements

1 Institute of Medicine, Dietary reference intakes for calcium and vitamin D, National Academies Press, 2011.
Calcium Controversy: What is one to do?

• Randomized controlled trials of calcium supplementation, (n = 26)\(^1\)
  – Pooled analysis reported 11% total fracture risk reduction, 14% reduction in vertebral fracture risk, but no effect on forearm or hip fracture
  – No effect of calcium supplements on any fracture in the largest of the trials with lowest risk of bias
  – Some trials have demonstrated harm, including increased heart attacks

• “Results suggest that widespread untargeted use of calcium supplements in older individuals is unlikely to result in meaningful reductions in incidence of fracture”

\(^1\)Bolland et al, Calcium intake and risk of fracture: systematic review. BMJ 2015.
Calcium Controversy: What about dietary intake?

- Observational data – mixed results, but 3 suggest possible harm, including increased hip fracture risk
  - Singapore Chinese Health Study
    - N=63,257 men and women
  - Swedish Mammography Cohort
    - N= 61,433 women
  - China Health and Nutrition Survey
    - N= 6,210

- “Nutritional emphasis should be placed on a moderate intake of calcium with an eye on habitual intake level in the prevention of osteoporotic fractures, rather than recommended universal intake of 1,000 -1,200 mg/d of dietary calcium”

1Fang et al, J Bone Miner Res, 2016.
Calcium Supplements and Adverse effects
Preliminary results reported at ASBMR 2019

• Results of two RCT’s of calcium supplements (1200 mg daily) on cardiovascular measures in older persons support their safety
  – Calcium Intake Fracture Outcome Study (n = 904)
  – Canadian study of calcium on vascular health (n = 121)

• Caveat: Multiple RCT’s of calcium demonstrate that constipation is a significant side effect and the demonstrated benefits are not 100% certain

Lewis J et al, JBMR 1168 (oral presentation, 2019)
VITAL Study
VITamin D and OmegA-3 Trial (VITAL)

- Vitamin D supplements and Omega-3 fatty acids are widely used

- VITAL tested whether vitamin D3 2,000 IU/day versus placebo and omega-3 oils 840 mg/day versus placebo prevented cancer and cardiovascular disease over 5.3 years of follow-up
  - 25,871 women (>55) and men (>50)
  - Factorial trial design: D3 and fish oil PBO, D3 PBO and fish oil, D3 and fish oil, D3 PBO and fish oil PBO

- No benefit seen with vitamin D in either cardiovascular or cancer outcomes

Manson et al, NEJM 2019
VITAL Study: Ancillary Studies
Vitamin D & fall risk
Preliminary results presented at ASBMR 2019

- Background: Earlier studies have suggested that vitamin D can reduce fall risk

- Study Design: RCT of 25,871 men and women, mean age 67 followed for 5.3 years

- Vitamin D3 2,000 IU vs. placebo

- Outcomes assessed (yearly assessment):
  - Number of falls
  - Number of falls resulting rom hospitalization
  - Number of injuries due to falls

LeBoff M et al, JBMR 1057, 2019
VITAL Study: Vitamin D and fall risk
Preliminary reported results ASBMR 2019

• >13,000 falls reported over 5+ years

• No differences were observed between groups in any fall measure

• **Take home message**: Supplemental vitamin D is not effective in reducing fall risk or falls outcomes in community-dwelling persons

*LeBoff Met al, JBMR 1057, 2019*
VITAL Study results: Vitamin D and bone turnover, bone density and bone structure
Preliminary results presented at ASBMR 2019

• Background: Vitamin D supplements are used widely to promote bone health, but the results are not conclusive

• Sub-cohort of 771 (47% women) VITAL participants
  – Followed for 2 years
  – Vitamin D 25-OH
  – DXA and pQCT were measured
  – 54% had low bone mass on DXA

• Results: no differences in bone measures between groups at 2 years

LeBoff et al, JBMR 1154, 2019
Vitamin D3 400, 4,000, and 10,000 IU daily for 3 years on Bone Density & Bone Strength Calgary Vitamin D Study:

Results:
- Higher dose vitamin D3 (>4,000 IU daily) associated with worse 3D bone density
- DXA total hip areal BMD no different among groups

<table>
<thead>
<tr>
<th>BMD site</th>
<th>400 IU</th>
<th>4000 IU</th>
<th>10,000 IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radius</td>
<td>-1.2%</td>
<td>-2.4%*</td>
<td>-3.5%*</td>
</tr>
<tr>
<td>Tibia</td>
<td>-0.4%</td>
<td>-1.0%</td>
<td>-1.7%*</td>
</tr>
</tbody>
</table>

Burt et al, JAMA 2019
Vitamin D3 400, 4,000, and 10,000 IU daily for 3 years on Bone Density & Bone Strength Calgary Vitamin D Study: Burt et al, JAMA 2019

Results:
• Higher dose vitamin D3 (>4,000 IU daily) associated with decreasing bone strength, though not statistically significant (p = 0.06 at the radius)

Authors’ conclusions:
• Among health adults, higher D supplementation resulted in statistically significantly lower radial BMD
• Tibial BMD was only lower in the highest dose group (10,000 IU daily)

Burt et al, JAMA 2019
VITAL Study: No benefit of vitamin D3 2,000 IU daily for any outcome

Calgary Study: suggestion that higher vitamin D >4,000 daily for 3 years could be associated with worse bone health

- Take home message may be that vitamin D is a threshold nutrient

IOM report, National Academy of Sciences; 2011
Summary: Calcium and vitamin D supplements
Do they help and/or can they harm?

- About 75% of Americans report using at least one dietary supplement (FDA report)
- Vitamin supplements are big business in the United States
  - $4 billion to $40 billion dollar industry over the past 25 years
- Recent studies published on calcium and vitamin D supplementation
  - Perhaps **no harm** in terms of markers of cardiovascular risk
  - Perhaps **harm** in terms of worse 3D bone structure with higher doses of vitamin D3
  - Perhaps **harm** in terms of altered calcium metabolism with higher doses of vitamin D3

*Sancar F, JAMA 2019*
What to do about calcium and vitamin D supplements? What should you recommend for patients?

- **For calcium, get it through the diet if possible**
  - Rationale:
    - RDA regulates the amount of calcium in food sources
    - FDA oversees the vitamin and dietary supplement industry and assumes they are safe without any testing
    - At least from the diet, you have a better idea of the amounts you are actually receiving

- **For vitamin D, supplement only if are insufficient (25(OH)D <30 ng/mL) and have osteoporosis concerns**
  - Rationale:
    - Sun exposure should be sufficient, but skin cancer a growing concern
    - Dietary sources of vitamin D are tougher to obtain
    - Wouldn’t suggest taking more than 4,000 IU daily based upon the latest data (consistent with IOM recommendations from 2011)
# Drugs for Osteoporosis 2020

<table>
<thead>
<tr>
<th>Anti-resorptive</th>
<th>Anabolic</th>
<th>Both</th>
</tr>
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<tbody>
<tr>
<td>Bisphosphonate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (Fosamax)</td>
<td>Teriparatide (Forteo)</td>
<td>Romosozumab (Evenity)</td>
</tr>
<tr>
<td>Risedronate (Actonel)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibandronate (Boniva)</td>
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<tr>
<td>Zolendronic Acid (Reclast)</td>
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<tr>
<td>Denosumab (Prolia)</td>
<td>Abaloparatide (Tymlos)</td>
<td></td>
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<tr>
<td>Estrogen</td>
<td></td>
<td></td>
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<tr>
<td>Raloxifene (Evista)</td>
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</table>
New Therapeutics: Abaloparatide

- Abaloparatide binds parathyroid receptor type 1
  - Anabolic effects with modest stimulation of bone resorption compared to teriparatide

- Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE)
  - Women, aged 49-86 years old T-score <-2.5 but >-5.0 & history of fracture (vertebral or low trauma non-vertebral)
  - 1° endpoint: 1 or more incident morphometric vertebral fracture
  - 2° endpoint: non-vertebral fracture
  - Exploratory endpoints: major osteoporotic fracture and clinical fracture

<table>
<thead>
<tr>
<th>Tymlos vs PBO</th>
<th>RH (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New vertebral fracture</td>
<td>0.14 (0.05-0.39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Non vertebral fracture</td>
<td>0.57 (0.32-1.00)</td>
<td>0.049</td>
</tr>
<tr>
<td>Major osteoporotic fracture</td>
<td>0.30 (0.15-0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical fracture*</td>
<td>0.57 (0.35-0.91)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Any fracture that would cause a patient to seek medical care

*Miller P et al, JAMA 2016*
New Therapeutics: Abaloparatide

Cosman F et al, May Clin Proceed 2018
New Therapeutics: Abaloparatide

- FDA approved in April 2017

- Adverse side effects (n = 2463 in Active trial; n = 1139 in Active Extend):
  - Most frequently reported:
    - Dizziness (10% vs. 6% in PBO & 7% in teriparatide group)
    - Nausea (8% vs. 3% in PBO & 5% in teriparatide group)
    - Palpitations (5% vs. 0.4% in PBO & 1.6% in teriparatide group)
  - Prespecified safety endpoint: Hypercalcemia > 10.7 mg/dL
    - 3.4% vs. 0.4% in PBO & 6.4% in teriparatide group

- Other key clinical points
  - Not approved for treatment in those who have already used teriparatide for 2 years
  - Does not need to refrigerated (as does teriparatide)
  - Pending FDA approval for treatment in men

Miller et al, JAMA 2016
New Therapeutics: Romosozumab

- Mechanism of action: Monoclonal antibody that inhibits sclerostin, increasing bone formation and decreasing bone resorption

- FRAME Study: 7,180 women, aged 55-90, with a T-score -2.5 to -3.5 at the total hip or femoral neck. Treated with Romosozumab vs. PBO followed by Denosumab

Cosman F et al, NEJM 2016
New Therapeutics: Romosozumab

- FRAME Study Results
  - Risk of new vertebral fracture 73% lower at 12 months, effect was rapid
  - Risk of clinical fracture was lower by 36% at 12 months (p = 0.008)

![Incidence of New Vertebral Fracture](chart)

Cosman F et al, NEJM 2016
New Therapeutics: Romosozumab

- ARCH Trial – Romosozumab versus alendronate, followed by alendronate
- 4093 women aged 55-90 with T-score of ≤-2.5 and ≥1 moderate or severe vertebral fracture or ≥2 mild vertebral fractures or proximal femur fracture and T-score ≤-2.0

Saag K et al, NEJM 2017
New Therapeutics: Romosozumab

- ARCH Trial Results: Women aged 55-90

**BENEFITS:**
- 37% risk reduction in new vertebral fractures at one year
- 27% risk reduction in clinical fractures
- 38% risk reduction in hip fractures

*Saag K et al, NEJM 2017*
New Therapeutics: Romosozumab

- FDA approved April 2019

- Adverse events
  - Osteonecrosis of the jaw (ONJ)
    - 2 cases in FRAME: 1 in romo group (1st 12 months) and 1 case in romo/dmab group (2nd 12 months)
    - 2 cases in ARCH: 1 case in alen/alen group and 1 case in romo/alen group during open label period (12-36 months)
  - Atypical femoral fracture (AFF)
    - 1 case in FRAME in romo/dmab group (2nd 12 months)
    - 6 cases in ARCH (4 in alen/alen group and 2 in romo/alen group)
  - Cardiovascular events
    - 44 vs. 41 in FRAME
    - 32 vs. 13 in ARCH (Black box warning)
Geriatrician’s Perspective: What is the goal here?

- **FRACTURE PREVENTION**
  - Diagnosis – identify those at high fracture risk
  - Medication – to decrease the risk of fractures
  - Fall prevention – to decrease the risk of fractures
    - 95% of hip fractures result from a fall

Many falls can be prevented. By making some changes, you can lower your chances of falling.

**Four things YOU can do to prevent falls:**

1. Exercise to improve your balance and strength
2. Have your health care provider review your medicines
3. Have your vision checked
4. Make your home safer

[Image of Fall Prevention Guide]
Geriatrician’s perspective:
Fall prevention is key to fracture prevention

• Facts about falls in older persons
  • About 30% of community-dwelling older adults report falling each year
  • 1 in 5 falls are injurious
    • Broken bones
    • Head injuries
  • A history of falls is a risk factor for future falls
Geriatrician’s perspective: Fall Prevention Strategies

- Multifactorial interventions (7 good quality trials)
  - Comprehensive geriatric assessment or fall risk factor assessment (balance, gait, vision, postural blood pressure, pulse)
  - Medication review
  - Environment (home hazards or personal needs)
  - Cognition/psychological health

- Exercise Interventions (n = 5 good quality trials)
  - Gait, balance and functional training
  - Group and/or home-based, most were 3 exercise sessions per week, followed for about 12 months

- USPSTF Key Conclusions
  - Overall, both multifactorial and exercise interventions work to decrease fall rates, but exercise does a bit better

Guirguis-Blake J et al, USPSTF Evidence Report JAMA 2018
Geriatrician’s perspective:
Fall prevention is key to fracture prevention

- Assessing fall risk is easy to do
  - Chair stand test
  - Semi-tandem stand
  - Tandem stand

- Recommend “exercise”
  - Conceptualize as being comfortable and aware in one’s own body
  - Discuss goals
  - Provide options
    - Tai Chi
    - Multimodal exercise – aerobic condition, strength, balance and flexibility
    - PT referral
Geriatrician’s perspective: Thinking about NNT (number needed to treat)

- First, to give some context:
  - Statin use to prevent one death over 1-6 years: NNT = 250, NNH = 197

<table>
<thead>
<tr>
<th>Osteoporosis Medication</th>
<th>Fall Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alendronate</td>
<td>Exercise/PT</td>
</tr>
<tr>
<td>NNT = 16</td>
<td>NNT = 9</td>
</tr>
<tr>
<td>NNH = 2,000</td>
<td>NNH = 0</td>
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<tr>
<td>Zolendronic acid</td>
<td>Multifactorial</td>
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<tr>
<td>NNT = 15</td>
<td>NNT = 11</td>
</tr>
<tr>
<td>NNH = n/s</td>
<td>NNH = 0</td>
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<tr>
<td>Denosumab</td>
<td>Medication review</td>
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<tr>
<td>NNT = 21</td>
<td>NNT = 7*</td>
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<tr>
<td>NNH = 353</td>
<td>NNH = n/a</td>
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<tr>
<td>Teriparatide</td>
<td>Home hazards</td>
</tr>
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<td>NNT = 11</td>
<td>NNT = 5</td>
</tr>
<tr>
<td>NNH = 33</td>
<td>NNH = 0</td>
</tr>
<tr>
<td>Abaloparatide</td>
<td>Syncope Rx</td>
</tr>
<tr>
<td>NNT = 28</td>
<td>NNT = 4</td>
</tr>
<tr>
<td>NNH = n/s</td>
<td>NNH = n/a</td>
</tr>
<tr>
<td>Raloxifene</td>
<td></td>
</tr>
<tr>
<td>NNT = 28</td>
<td></td>
</tr>
<tr>
<td>NNH = 250</td>
<td></td>
</tr>
</tbody>
</table>

*Result not statistically significant

Closing Remarks:
Comparing osteoporosis to another common age-related disease

• Osteoporosis is like hypertension
  – It is common affecting approximately >50% of older adults
  – Silent until the disease manifests
  – Sequelae from a hip fracture and stroke have long-term health and lifestyle implications

• Osteoporosis is not like hypertension
  – Diagnosis can be made in several ways
    • DXA BMD
    • Fragility fracture, defined as a fracture occurring from standing height or less
    • Trabecular bone score, CT scan, ultrasound technologies, etc
  – Pharmacologic treatment is not for life
Closing Remarks: Treatment

• Osteoporosis is like hypertension
  – Lifestyle choices can effectively help avoid the consequences of osteoporosis/uncontrolled high blood pressure
  – Multiple choices for drug treatment available

• Osteoporosis is not like hypertension
  – An astute clinician can make a presumptive diagnosis with simple observation without touching the patient
  – The NNT is lower to prevent vertebral fractures (n = 16) versus the NNT to prevent stroke (n = 120)
Closing Remarks: Pharmacologic Treatment

- Bisphosphonates still # 1 for osteoporosis treatment
  - Alendronate (Fosamax) works
    * FDA approved in 1995
    * Compliance due to dosing and side effects make this drug less effective
  - Zolendronic Acid (Reclast)
    * Compliance better assured
    * Easier dosing regimen (once yearly to once every 18 months)

- Multiple studies suggest a mortality benefit in those who take bisphosphonates
Summary: Fracture Prevention Challenges

- Competing priorities as we age
- Misinformation/Mistrust
- Patients who do fracture do not necessarily attribute the fracture to an underlying disease (e.g. osteoporosis)
- Not as simple as prescribing a medication without keeping track of timing of treatment
- PMD’s have a lot to manage in a short clinic visit
Summary: Fracture Prevention
Balancing the Benefits Against the Risks

• Fall prevention is key with little associated harms

• Benefits of FDA approved osteoporosis drug treatment generally outweigh harms in those at high fracture risk. For example, those with:
  – Previous history of fracture(s)
  – Very low bone density/thin build
  – Unsteady gait
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Questions?

"That's not the kind of bone loss we talk about."

off the mark

by Mark Parisi

there are bones in our bodies?

THE BIG FREAK-OUT IN A PUPPY'S LIFE
New Therapeutics: Romosozumab

- BRIDGE study
  - 245 men aged 55-90
  - T-score ≤ -2.5 or ≤ -1.5 and previous fragility fracture
  - Randomized 2:1

Lewiecki M et al, J Clin Endo Metab 2018
New Therapeutics: Romosozumab

• Summary of adverse events reported in 3 trials, continued
  
  • Most concerning:
    • Cardiac ischemic events
      • FRAME trial: 44 in romo vs. 41 in PBO at one year*
      • FRAME trial: 82 in romo/dmab vs. 79 in PBO/dmab at 2 years
      • ARCH trial: 16 romo vs. 6 alen in at one year
      • ARCH trial: 30 romo/alen vs. 20 alen/alen during open label period
      • BRIDGE trial: 3 romo vs. 0 PBO in 12 months
    
    • Cerebrovascular events
      • ARCH trial: 16 romo vs 7 alen at one year
      • ARCH trial 45 romo/alen vs. 27 alen/alen during open label period
      • BRIDGE trial: 3 romo vs. 1 PBO in 12 months
  
  • FDA approved in April 2019

*FRAME combined all adjudicated serious cardiovascular events into one category
VITAL Study:
What were the Vitamin D levels in these participants?

- 15,804 had vitamin 25(OH)D measured at baseline and 1 year later

- Mean 25(OH)D was 30.8 ng/mL
  - 12.7% had levels <20 ng/mL
  - 32.2% had levels <30 ng/mL

- Increased by 11.9 ng/mL (40%) in treatment group

- Decreased by 0.7 ng/mL in placebo group

Luttman-Gibson H et al, Contemp Clin Trials, 2019
Geriatrician’s perspective: Exercise may work best

• But, does fall prevention prevent fractures?

• What is the trial related evidence for decrease in important health related outcomes?
  • Fall reduction and reduced injury
    • 5 RCTs (n = 2776)
    • Reduced injury by about 10-27%
  • Fall reduction and fracture outcomes
    • 3 RCTs (n = 2047)
    • Reduced rate of fall related fractures by about 8-74%
  • Fall reduction and mortality
    • 11 RCT’s (n = 4263)
    • No significant risk reduction

Guirguis-Blake J et al, USPSTF Evidence Report JAMA 2018